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Archives of Internal Medicine

VOLUME 37 FEBRUARY, 1926 NUMBER 2

THE RELATION OF ALBUMINURIA TO PROTEIN REQUIREMENT IN NEPHRITIS *

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AND

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The proper composition of nephritic diets has been a continuous source of controversy. Since it was first demonstrated that certain patients with renal disease retained nitrogenous waste products, it has become general practice to restrict the protein of the diet in all cases of nephritis. This tendency received a further impetus from the misconception that urea and other protein metabolites that accumulated in the blood of persons with impairment of kidney function were themselves responsible for some of the symptoms of uremia. The general burden of evidence goes to prove that this is not the case and that urea concentrations quite as great as those encountered in the blood of some patients with nephritis are incapable of producing anything resembling the uremic syndrome. An extended investigation of the nonprotein nitrogenous constituents of the blood in nephritis has also revealed the fact that retention of these waste products may be, and usually is, lacking or an insignificant feature in certain types of nephritis, and notably in those chronic or subacute types which are characterized especially by edema which is not due to cardiac decompensation, the parenchymatous nephritis of older terminologies, the nephroses and the nephrotic forms of glomerulonephritis of Volhard and Fahr.[1]

The failure to find a justification for the indiscriminate use of low protein diets in the results of chemical analysis of blood has not convinced the advocates of this therapeutic procedure of its error. The theory that the end products of protein catabolism are renal irritants or

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1. Volhard, Franz: Die doppelseitigen hämatogenen Nierenkrankheiten, 1918. Volhard, Franz; and Fahr, T.: Die Brightsche Nierenkrankheiten, Berlin, 1914. Fahr, T.: Virchows Arch. f. path. Anat. **239**:32, 1922.

that by relieving the kidney of the necessity of excreting these products the organ is rested has furnished new pretexts for its continuation. Some support for the idea that proteins are deleterious has been given by Newburgh,[2] who has produced nephritis in rabbits by the administration of diets containing excessive amounts of protein. The fact that the administration of excessive protein to a vegetarian animal results in the development of nephritis is no good evidence that ordinary amounts of protein will have a similar effect on an omnivorous animal.

If protein waste products are injurious to the kidney or strain it, and this is by no means established, the rational procedure is to give not an excessively low protein diet, but a diet that will reduce the nitrogen metabolism to a minimum; the two are not necessarily synonymous. Even this alone is not sufficient. Complete protein starvation with the administration of large amounts of carbohydrate and fat will effect an extreme reduction of nitrogen metabolism and has been employed as a temporary expedient in the treatment of uremia. It is not, however, a procedure that can be continued indefinitely, because protein wastage is itself attended with serious results. Nephritis is a chronic disease and treatment must, therefore, be so regulated that it can be continued for an indefinite period. It is essential that reduction of protein be controlled to insure the patient against the effects of protein starvation. In other words a negative nitrogen balance must be avoided. This is possible only if a sufficient minimum of protein and an adequate amount of carbohydrate are given.

The literature is strangely lacking in studies of nitrogen metabolism directed to the determination of the actual protein and caloric requirements of nephritic patients. Mosenthal and Richards [3] and others have shown that under certain conditions there may be an increased destruction of protein in the body. They also have pointed out that a negative nitrogen balance is often associated with a rising blood nonprotein nitrogen, while, when the nitrogen output diminishes, the blood nonprotein nitrogen also may fall. In these cases the alterations of blood chemistry are as much due to changes of metabolism as they are to renal impermeability and the effect of these metabolic changes cannot safely be ignored in the regulation of diet.

Another factor also has been largely neglected, albuminuria. Albuminuria represents the excretion of preformed protein which has, presumably, played no part in the metabolic processes of the body and served no useful purpose in the economy of the organism. It is generally believed that this protein is derived from the serum albumin to

2. Newburgh, L. H.: The Production of Bright's Disease by Feeding High Protein Diets, Arch. Int. Med. **24**:359 (Oct.) 1919.

3. Mosenthal, H. O., and Richards, A. C.: The Interpretation of a Positive Nitrogen Balance in Nephritis, Arch. Int. Med. **17**:329 (Feb.) 1916.

which, under certain circumstances, the kidneys become permeable. This loss of serum albumin may play an important part in the production of the low proteins of those forms of nephritis in which albuminuria is an especially striking symptom, the parenchymatous nephritides, the nephroses or the nephrotic types of glomerulonephritis. Some disturbance of the mechanism for the regeneration of the serum proteins also may be active. There is no reason for believing that the nitrogen of urine albumin plays any rôle in the normal protein metabolism of the body nor is there any convincing evidence that the metabolism of patients with albuminuria is especially low. It is fair to assume, then, that such patients will excrete the usual amount of nonprotein nitrogen and in addition an amount equivalent to the proteinuria.

It is reasonably certain that the diet can be so adjusted as to provide for the nonprotein nitrogen loss. How much excess protein will be required to replace the albumin excreted is less certain. In fact it is not possible to say *a priori* whether it can be replaced at all. If an ordinary person is fed an excess of protein the surplus accumulates in the body only to a limited extent and almost immediately the nitrogen excretion rises to the level of the nitrogen intake and equilibrium is established. In this case all the nitrogen is broken down and excreted in the form of urea and the other common nitrogenous end products.

Epstein,[4] realizing the part that protein loss probably plays in these cases and believing that the low concentration of plasma proteins was itself partly responsible for the appearance of edema, long since advocated high protein diets. Clinical observation convinced him that such diets were distinctly beneficial. Others have been less favorably impressed by Epstein's diets. The opinion of Linder, Lundsgaard and Van Slyke [5] is representative of the conclusions that have been reached by those who have given the subject serious study and thought. These authors believe that diets should contain an adequate but not excessive amount of protein. Unfortunately we are quite ignorant of what an adequate amount of protein may be.

Recent work of McLean [6] and Wordley [7] also has an interesting bearing on the problem. These authors believe that the beneficial effect of high proteins is largely due to the diuretic effect of the increased

4. Epstein, A. A.: Concerning the Causation of Edema in Chronic Parenchymatous Nephritis; Method for Its Alleviation, Am. J. M. Sc. **154**:638 (Nov.) 1917.

5. Linder, G. C.; Lundsgaard, Christen; and Van Slyke, D. D.: The Concentration of the Plasma Proteins in Nephritis, J. Exper. Med. **39**:887 (June) 1924.

6. McLean, Hugh: Modern Methods in the Diagnosis and Treatment of Renal Disease, London, 1924.

7. Wordley, E.: The Effect of High Protein Diet on Albuminuria and Blood Urea in Cases of Nephritis, Quart. J. Med. **14**:88 (Oct.) 1920.

urea formed from them. They advocate the administration of urea itself. Although this will seem to many dangerously unorthodox, the clinical results obtained by them with doses ranging from 20 to 45 gm. of urea a day in cases of nephritis with edema, but without any tendency to nitrogen retention, are worthy of consideration.

The work presented here was undertaken in an attempt to learn something of the nitrogen metabolism in nephritis, to establish more definitely the nitrogen requirements of the disease, to find out whether, and how, protein lost as albumin could be replaced, and to study the effect of feeding on the level of the plasma proteins, the clinical aspects of the disease and the chemical composition of the blood.

This paper deals with a study of the protein metabolism in the types of nephritis characterized especially by the occurrence of edema (which is not referable to cardiac decompensation), profuse albuminuria and reduction of the plasma proteins, with little tendency to the development of nitrogen retention, hypertension and its complications, retinitis or uremia except as terminal symptoms. This is the type of nephritis that has long been known as chronic or subacute parenchymatous, and it includes Volhard and Fahr's nephrosis as well as their nephrotic form of glomerulonephritis. The failure to distinguish between these two diseases does not imply that the authors are convinced that such a distinction is unwarranted. On this subject they are entirely open minded. For reasons that will appear, however, they do feel that the distinction is clinically difficult or impracticable in the majority of instances.

Among adults, to whom this study is almost entirely confined, clear cut examples of this disease are comparatively rare. The investigations do not, therefore, include a large number of cases. A variable amount of work was done on each patient, depending largely on the character of the individual. As these studies were carried out in the general medical wards, in large part while the metabolism department was still in process of development, much of the work done had to be discarded because of faulty collections of urine or the administration of improper diets. All data concerning the accuracy of which there was room for reasonable doubt have been discarded. The amount that remains represents a pitifully small fraction of the work that was done but is, we believe, reliable in all essential respects.

PROCEDURE

Diets were prepared in the special diet kitchen of the hospital. Protein and calories were estimated from the usual Atwater and Bryant[8] tables. Chlorid was calculated by means of the analyses of Sherman.[9] In all probability the

8. Atwater, W. O., and Bryant, A. P.: Chemical Composition of American Food Materials, Bull. U. S. Dept. Agriculture, No. 28, 1906.

9. Sherman, H. C.: Chemistry of Food and Nutrition, Ed. 2, 1924, New York, Macmillan Company, p. 421.

chlorid values given are minimal. Occasionally it proved necessary to use canned vegetables. Whenever possible these were washed once and the water discarded. Although this probably failed to remove all the salt, further washing seemed inadvisable. Fluids were carefully measured and the amounts administered were recorded when they were given by the nurse in charge of the case. Urine specimens were collected in bottles that contained a small amount of toluene and sent to the hospital laboratory of the department of internal medicine, where they were accurately measured and analyzed. The cooperation and interest of the patient was enlisted in the recording of fluids and the collection of urine. Patients were weighed at the same time every day.

Total urinary nitrogen was estimated by the usual Kjeldahl procedure. For the determination of nonprotein nitrogen a fraction of the urine was treated with an equal amount of 10 per cent. trichloracetic acid solution. The precipitated protein was filtered off and an aliquot portion of the filtrate was then analyzed for nitrogen. Salt was estimated by the usual Volhard-Harvey titration.

Blood was withdrawn from an artery or vein, usually before breakfast, and was studied by methods outlined in another article. Proteins were determined on 0.5 c.c. samples of plasma or serum by the ordinary Kjeldahl procedure. In all the earlier studies plasma was employed; in the more recent experiments serum was used. In the interests of economy blood and not plasma or serum was taken for the estimation of nonprotein nitrogen.

In the tables the first column shows the caloric value of the diet and the second the fluid intake. The latter includes all obvious fluids given at or between meals, but not the fluid content of solid or semisolid foods. In Column 3 is given the urine volume, while Column 4 presents the fluid balance as intake — output. In the next column appears the weight in kilograms. In each case the weight given for a certain day is the one obtained the next morning and, therefore, indicates the result of the treatment of the day in question. The nitrogen intake is obtained by dividing the protein of the diet by 6.25. The nitrogen output represents only the amount excreted in the urine. The difference, which appears in the next column, indicates the excess of food nitrogen over urinary nitrogen. Nonprotein nitrogen of the urine was estimated only in a few cases. This is a measure of the actual nitrogen catabolism. The difference between the food nitrogen and the urinary nonprotein nitrogen represents the amount of protein given in excess of the actual metabolic needs of the individual. Protein lost as albumin is obtained by subtracting urinary nonprotein nitrogen from urinary total nitrogen and multiplying the difference by 6.25. The difference between chlorid intake and output has been given as a general indication of the trend of the chlorid balance. Chlorid has been expressed in the usual manner, as sodium chlorid. When it was desired to increase the chlorid of the diet the additional salt was given to the patient in capsules to be taken in that form or to be spread on the food, according to his tastes. When ammonium chlorid or urea was given the additional nitrogen and chlorid from these sources has been estimated and added to the figures for daily intake.

$$\text{1 gm. of ammonium chlorid} = \frac{14}{53.5} = 0.262 \text{ gm. of nitrogen and } \frac{58.5}{53.5} = 0.262 \text{ gm. of sodium chlorid}$$

$$\text{1 gm. of urea} = \frac{28}{60} = 0.467 \text{ gm. of nitrogen.}$$

REPORT OF CASES

CASE 1.—A Polish man, aged 29, was admitted to the hospital, Oct. 14, 1924, complaining of dyspnea, swelling of the legs and abdomen and lumbar pain.

About two years earlier he had an attack of rheumatism involving the wrists, ankles and shoulders, which ran a remittent course for three or four months, shifting from joint to joint. Shortly after the rheumatism disappeared,

the ankles began to swell and the legs and abdomen later became involved. At the same time he noticed that his urine was bloody and he developed frequency of urination and pain in the lumbar region. All these symptoms persisted with slight remissions and exacerbations. The latter occurred especially when he caught cold or had a sore throat. During the periods of increasing edema, there was weakness, general irritability, sleeplessness and frequent night sweats. For six months dizziness, occasional frontal headaches and dyspnea on exertion, and for three or four months a nonproductive cough and a tendency to gastric distention after eating also had troubled him.

As a child in Poland he had typhus; he could remember no other serious illnesses and none of the usual childhood diseases. For some years he had frequent attacks of tonsillitis. In 1918, while he was serving in the French army, one tonsil was removed. At that time he was ill for about a month and received three therapeutic injections of some kind, apparently not mercury or arsenicals. His second tonsil was removed about six months before he entered the hospital. His habits were quite exemplary and he said that he had no venereal disease.

When he entered the hospital he appeared chronically ill; he was pale and sallow, with slight puffiness of the face. The temperature, pulse and respirations were normal. His heart was slightly enlarged to the left and a loud systolic murmur was audible over the whole precordium. The systolic blood pressure was 155, the diastolic 95. The peripheral vessels were soft. At the base of both lungs resonance and breath sounds were impaired and there were signs of slight accumulation of fluid in the peritoneal cavity. The liver edge was felt just below the costal margin and the edge of the spleen descended 2 cm. below the costal margin on deep inspiration. There was considerable tenderness to deep palpation and percussion in both costovertebral angles, but the kidneys did not seem to be enlarged. Over the whole trunk there was moderate pitting edema, and a more striking edema of the lower extremities.

Ophthalmoscopic examination revealed slight irregularity in the outlines of the arteries. The blood Wassermann reaction was negative. Phenolsulphonephthalein excretion, October 15, was 45 per cent. in two hours and ten minutes. Blood cultures on October 15 and 19 were sterile. Urine cultures also proved sterile. Roentgen-ray examination of the heart revealed slight left sided enlargement. The basal metabolism, October 16, was 12.5 per cent. above normal. On admission the urine contained a large amount of albumin, many hyaline and granular casts and numerous red and white blood cells.

The patient was immediately ordered a salt-poor diet containing 50 gm. of protein and 2,200 calories, with fluids restricted to 2,000 c.c. This resulted in diuresis. By October 20 most of the subcutaneous edema and all signs of ascites had disappeared. The spleen was no longer palpable, although the area of splenic dulness was still enlarged. October 25, no signs of edema could be found. The character of the urine was, however, unchanged. During this period and until the middle of November, in spite of the fact that the patient was losing weight, the relation of fluid intake to urine output indicated a considerable positive water balance. The explanation probably lies in the fact that he had frequent, profuse night sweats.

Because he had a constant negative nitrogen balance with a diminishing blood nonprotein nitrogen, his diet was increased to contain 75 gm. of protein and 2,500 calories, November 24. On this diet he began to store nitrogen but the nonprotein nitrogen of the blood rose.

In view of a continuous negative salt balance 5 gm. of sodium chlorid was given daily, beginning October 28. On this regimen the weight again increased and considerable salt was retained in the body. It must be mentioned that during this period he developed some temperature, associated with backache and gross hematuria.

November 8, the salt-poor diet was resumed. By November 13 the blood nonprotein nitrogen had diminished again without any reduction of dietary

protein and in spite of a positive nitrogen balance. He was then given a course of ammonium chlorid therapy. In spite of a severe acidosis this produced no considerable diuresis, but the albuminuria increased in severity. For three days after the ammonium chlorid was discontinued he suffered from epigastric discomfort that prevented him from eating his full diet. At this time he developed a definite diuresis.

November 22, the protein of the diet was reduced to 60 gm., and it was kept at this level until he left the hospital. Under this regimen he stored nitrogen constantly. At first he lost weight, probably the residium of his edema. November 29, the caloric value of the diet was increased to 3,500 calories. Under these conditions his weight increased slightly and he stored nitrogen constantly in spite of the fact that he remained free from edema and that the blood nonprotein nitrogen diminished.

The urine albumin, casts and cells decreased somewhat during this period. He was discharged from the hospital December 24.

From time to time his temperature rose somewhat above normal, usually with symptoms of upper respiratory tract infection. October 26, it went up to 100.4 degrees F.; November 8 and again on December 17, as high as 101; and on each of the last four days in the hospital it reached 100 F.

At the time of admission he presented a considerable degree of anemia of the secondary type. The hemoglobin determined gasometrically by the Van Slyke method was only 53 per cent. (9.9 per cent. by volume oxygen capacity), the cell volume 24.8 per cent. by volume, and the red blood cell count about 4 million. The blood picture varied somewhat, but at the time of discharge was distinctly improved. The hemoglobin had risen to 65 per cent. and the cell volume to 28.4 per cent. by volume.

The specific gravity of the twenty-four hour specimen varied from 1.009 to 1.024. Throughout the course of the disease his urine contained large amounts of albumin and casts and some red blood cells and leukocytes. The number of cells varied greatly. The metabolism record appears in Table 1.

During the whole time he was studied in the hospital, sixty-four days, he received altogether protein and ammonium chlorid equivalent to 688.3 gm. of nitrogen. Over the same period he excreted in the urine 568.5 gm. of nitrogen, giving a positive balance of 119.8 gm. This does not, of course, represent the actual amount of protein stored because the amount of nitrogen lost in the stools has been neglected. The latter usually amounts to about 10 per cent. of the food protein. The actual food protein amounted to the total nitrogen intake minus 18.1 gm. of nitrogen which was given as ammonium chlorid, or $688.3-18.1=670.2$. Therefore, $670.2\times 0.9=605=$ the grams of nitrogen actually available to the body as useful protein. The nitrogen of the ammonium chlorid was presumably recovered in the urine as urea and ammonium salts. In calculating the nitrogen balance it is therefore necessary to subtract the same amount from the urinary nitrogen. The urinary nitrogen actually observed was 568.5 gm. Corrected for ammonium chlorid and urea this becomes $568.1-18.1=550.4$ gm. The nitrogen balance is, therefore, $605.0-550.4=54.6$ gm. of nitrogen retained, the equivalent of $54.6\times 6.25=341$ gm. of protein, or, dividing by the number of days, $\frac{341}{64}=5.3$ gm. of protein per day. In other words, by the administration of an average of $\frac{670.2\times 6.25}{64}=65.4$ gm. of protein per day, the patient was enabled to store 5.3 gm. per day for a period of more than two months.

When he entered the hospital the patient had evident edema and part of his weight, 71.8 kg., was probably made up by tissue that was relatively inactive from a metabolic standpoint. His weight at the time of discharge, 64.5 kg., represents more accurately the amount of functioning tissue. In calculating the rate of metabolism this terminal weight has, therefore, been employed throughout this study. On this basis the protein given amounted to $\frac{65.4}{64.5}=1.02$ gm. per kilogram a day.

TABLE 1.—*Data in Case 1*

Date		Food, Calories	Fluids: Intake, C.c.	Fluids: Urine, C.c.	Fluids: Balance, C.c.	Weight, Kg.	Total Nitrogen: Intake, Gm.	Total Nitrogen: Urine, Gm.	Total Nitrogen: Balance, Gm.	Urine Nonprotein Nitrogen, Gm.	Protein Lost as Albumin, Gm.	Chlorid as Sodium Chlorid: Intake, Gm.	Chlorid as Sodium Chlorid: Output, Gm.	Chlorid as Sodium Chlorid: Balance, Gm.	Blood Nonprotein Nitrogen, Mg. per 100 C.c.	Plasma Protein, per Cent.	Special Medication
Oct.	16	2,279	2,000	840	1,160	71.5	8.52	7.13	1.39	5.62	9.4	1.07	4.23	—3.16	43	4.56	
	17	2,250	2,100	1,350	750	70.3	8.05	11.83	—3.78	9.31	15.7	1.35	8.71	—7.36	..	....	
	18	2,259	1,800	760	1,040	69.9	8.19	6.69	1.50	5.36	8.3	1.21	5.39	—4.18	..	....	
	19	2,259	2,000	1,620	380	69.6	8.19	17.26	—9.07	12.65	28.8	1.21	9.17	—7.96	..	....	
	20	2,259	2,000	1,320	680	69.1	8.19	9.49	—1.30	7.10	14.9	1.21	5.52	—4.31	..	....	
	21	2,259	2,000	490	1,510	68.8	8.19	4.32	3.87	3.22	16.9	1.21	2.19	—0.98	.	....	
	22	2,259	2,000	1,110	890	67.2	8.19	8.83	—0.64	6.76	12.9	1.21	5.16	—3.95	..	....	
	23	2,259	2,000	940	1,060	66.8	8.19	9.52	—1.33	7.10	15.1	1.21	3.93	—2.72	35	4 38	
	24	2,564	1,920	1,020	900	66.0	12.16	10.62	1.54	8.03	16.2	1.19	4.31	—3.12	..	....	
	25	2,539	2,000	980	1,020	65.8	11.76	10.68	1.08	8.08	16.2	1.05	3.65	—2.60	..	....	
	26	2,536	2,100	870	1,230	....	12.30	9.60	2.70	7.22	14.9	1.30	2.87	—1.57	..	....	
	27	2,539	2,000	890	1,110	64.4	11.76	10.32	1.44	7.87	15.3	1.05	3.26	—2.21	..	....	
	28	2,702	2,000	515	1,485	64.8	12.51	5.81	6.70	4.51	8.1	6.10	1.61	4.49	51	3.94	
	29	2,537	1,820	860	960	64.9	12.11	9.33	2.78	7.29	12.7	6.21	4.80	1.41	..	....	
	30	2,536	2,030	1,060	970	64.4	12.30	12.88	—0.58	9.50	20.6	6.30	4.35	1.95	..	....	
	31	2,558	2,030	1,050	980	65.7	12.41	11.44	0.97	9.00	15.2	6.30	5.25	1.05	..	....	
Nov.	1	2,564	2,000	650	1,350	63.2	12.16	7.55	4.61	5.73	11.4	6.19	3.99	2.20	..	....	
	2	2,537	2,000	760	1,240	65.7	12.17	8.48	3.63	6.59	11.8	6.21	3.55	2.66	..	....	
	3	2,558	2,000	670	1,330	65.5	12.41	7.61	4.80	6.30	8.2	6.30	2.81	3.49	..	....	
	4	2,667	2,000	760	1,240	....	8.52	9.37	—0.85	7.03	14.6	5.86	3.33	2.53	..	....	
	5	2,784	2,020	660	1,360	65.3	11.85	7.99	3.86	5.93	12.9	6.03	3.43	2.60	..	....	
	6	2,764	2,990	900	2,090	66.6	12.01	10.67	1.34	8.16	15.7	6.16	4.95	1.21	53	3.62	
	7	2,771	3,030	900	2,130	67.3	12.32	10.39	1.93	7.79	16.2	6.04	4.52	1.52	..	....	
	8	2,764	1,980	810	1,170	68.0	12.01	9.56	2.45	8.79	4.8	1.16	4.02	—2.86	..	....	
	9	2,771	2,070	700	1,370	68.0	12.32	8.32	4.00	6.16	13.5	1.04	2.91	—1.87	..	....	
	10	2,774	2,130	1,050	1,080	68.0	12.34	11.68	0.66	8.97	16.9	1.08	4.42	—3.34	..	....	
	11	2,769	2,090	750	1,340	68.1	12.32	8.69	3.63	6.52	13.6	1.15	3.27	—2.12	..	....	

	12	2,762	2,000	800	1,200	67.1	12.34	9.64	2.70	7.21	15.2	1.32	3.70	—2.28	..	....	
	13	2,774	2,020	940	1,080	67.5	14.96	10.89	4.07	8.24	16.6	12.01	4.95	7.06	43	4.17	Ammonium chlorid, 10 gm.
	14	2,930	2,000	1,170	830	67.5	14.55	12.68	1.87	9.68	18.7	12.17	6.86	5.31	..	....	Ammonium chlorid, 10 gm.
	15	2,769	2,000	1,340	660	67.5	16.25	13.78	2.47	10.60	23.6	17.55	8.55	9.00	..	....	Ammonium chlorid, 15 gm.
	16	2,737	2,000	1,500	500	67.9	12.45	13.43	—0.98	10.77	16.6	17.26	8.26	9.00	..	....	Ammonium chlorid, 15 gm.
	17	2,690	2,000	1,380	620	68.7	15.86	10.96	4.90	7.64	20.8	11.44	7.82	9.62	..	....	Ammonium chlorid, 4 gm.
	18	2,769	2,000	1,290	710	68.2	13.36	10.17	3.19	7.03	19.6	5.53	7.28	—1.75	47	4.39	
	19	2,506	2,000	1,060	940	67.1	9.84	8.62	1.22	6.08	16.2	1.06	5.47	—4.41	..	....	
	20	2,225	2,000	1,400	600	65.5	11.28	9.99	1.29	7.44	15.9	1.00	7.17	—6.17	..	....	
	21	2,531	2,000	1,980	20	64.5	10.77	10.19	0.58	9.65	3.4	0.95	9.72	—8.77	..	....	
	22	2,871	2,000	2,340	—340	64.5	9.55	10.86	—1.31	8.22	16.5	0.99	11.51	—10.52	..	....	
	23	2,835	2,000	2,160	—160	63.2	9.63	10.25	—0.62	7.58	16.7	0.88	10.00	—9.12	..	....	
	24	2,812	2,000	1,740	260	62.5	9.48	9.64	—0.16	6.68	18.5	0.92	8.12	—7.20	..	....	
	25	2,835	2,000	1,420	580	62.7	9.60	9.02	0.58	6.31	16.9	0.88	6.42	—5.54	32	4.07	
	26	2,871	2,000	1,480	520	62.5	9.55	9.03	0.52	6.41	16.4	0.99	7.07	—6.08	..	.. .	
	27	2,831	2,000	1,270	730	62.5	9.82	8.54	1.28	6.11	15.2	0.98	5.07	—4.09	..	....	
	28	3,661	2,000	1,120	880	62.5	9.85	7.03	2.82	4.96	12.9	1.04	3.70	—2.66	..	....	
	29	3,538	2,000	1,260	740	62.6	9.96	7.10	2.86	5.35	10.9	1.10	3.72	—2.62	..	....	
	30	3,521	2,000	910	1,090	62.7	10.16	6.74	3.42	4.92	11.4	1.29	3.62	—2.33	..	....	
Dec.	1	3,618	2,000	940	1,060	63.2	10.45	6.37	4.08	4.74	10.2	0.98	3.86	—2.88	..	....	
	2	3,487	2,000	1,540	460	62.9	9.60	7.16	2.44	5.53	10.2	1.14	4.73	—3.59	..	.. .	
	3	3,538	2,000	1,360	640	63.4	9.96	6.84	3.12	5.06	11.1	1.10	4.04	—2.94	..	....	
	4	3,487	2,000	1,240	760	63.4	9.60	6.77	2.83	5.27	9.4	1.14	3.11	—1.97	..	....	
	5	3,531	2,000	1,580	420	63.2	9.92	6.57	3.35	5.70	5.4	1.02	3.76	—2.74	..	....	
	6	3,618	2,000	1,680	320	63.5	10.45	8.28	2.17	5.88	15.0	0.98	3.39	—2.41	33	4.20	
	7	3,487	2,000	1,420	580	63.4	9.60	6.29	3.31	4.96	8.3	1.14	3.31	—2.17	..	.. .	
	8	3,531	2,000	1,440	560	63.3	9.92	8.02	1.90	6.18	11.5	1.02	3.95	—2.93	..	....	
	9	3,521	2,000	1,220	780	63.5	10.16	7.20	2.96	4.85	14.6	4.29	3.62	0.67	..	....	
	10	3,538	2,000	980	1,020	64.2	9.96	7.06	2.90	5.32	10.9	4.10	4.08	0.02	..	....	
	11	3,487	2,000	980	1,020	64.2	9.60	6.79	2.81	5.05	10.9	1.14	4.63	—3.49	..	....	
	12	3,531	2,000	1,060	940	64.0	9.92	6.37	3.55	4.65	10.7	1.02	3.88	—2.86	..	....	
	13	3,521	2,000	1,160	840	64.0	10.16	6.79	3.37	5.12	10.4	1.29	4.31	—3.02	..	....	
	14	3,538	2,000	1,300	700	64.7	9.96	6.85	3.11	5.02	11.4	1.10	3.90	—2.80	..	....	
	15	3,521	2,000	1,220	780	64.6	10.16	6.66	3.50	4.98	10.5	1.29	3.27	—1.98	..	....	
	16	3,487	2,000	1,220	780	64.1	9.60	6.48	2.13	4.79	10.6	1.14	2.89	—1.75	..	....	
	17	3,618	2,000	770	1,230	64.0	10.45	5.76	4.69	4.28	9.2	0.98	2.52	—1.54	..	....	
	18	3,521	2,000	1,420	580	64.5	10.16	7.59	2.57	6.01	9.9	1.29	3.81	—2.52	28	....	

The amount of protein lost as albumin in the urine amounted to 862.5 gm., or $\frac{862.5}{64} = 13.5$ gm. a day. By the administration of 1.02 gm. of protein the patient was enabled to maintain nitrogen equilibrium in spite of the continuous loss of 13.5 gm. of protein a day as albumin, and to store 5.3 gm. of protein a day. This calculation is probably minimal. The nitrogen output was partly due merely to sweeping out of the excessive nonprotein nitrogen of the blood and partly due to the loss of nonprotein nitrogen in the edema fluid that was lost through diuresis.

The actual nitrogenous metabolism of the individual is expressed not by the total nitrogen output, but by the excretion of nonprotein nitrogen. This amounted altogether to 430.3 gm. in sixty-four days. From this must be subtracted the nitrogen given as ammonium chlorid and the amount due merely to the loss of edema fluid and the reduction of the blood and tissue nonprotein nitrogen. For the purpose of gaining some estimate of the value of the two latter factors one may assume that the nonprotein nitrogen is comparatively evenly distributed throughout the aqueous phase of tissues and body fluids. Under normal circumstances about 70 per cent. of the body weight is composed of water. The concentration of water in edema fluid is usually much greater, at least 90 per cent. If the final weight of the patient, 64.5 kg., is considered to represent normal tissue and weight in excess of this edema, one may calculate the nonprotein nitrogen content of the whole body at the beginning of the experiment as 70 per cent. of the final weight plus 90 per cent. of the difference between initial and final weights, together multiplied by the initial blood nonprotein nitrogen, or $0.48\ [(0.7 \times 64.5) + (0.9 \times \overline{71.8 - 64.5})]$, and the nonprotein nitrogen content of the body at the end of the experiment at 70 per cent. of the final weight multiplied by the final blood nonprotein nitrogen, or $(0.7 \times 64.5)\ 0.28$. The difference between these two represents what may be termed the extra metabolic loss of nonprotein nitrogen. This equals $0.48\ [(0.7 \times 64.5) \times (0.9 \times \overline{71.8 - 64.5})] - 0.28\ (0.7 \times 64.5)$. This can be simplified to the form $(0.48 - 0.28)\ (0.7 \times 64.5) + (71.8 - 64.5)\ (0.9 \times 0.48)$, i. e., 70 per cent. of the final weight multiplied by the change of nonprotein nitrogen plus 90 per cent. of the change of weight multiplied by the initial nonprotein nitrogen. This is equal, in this case, to 12.2 gm. If this is added to the ammonium chlorid nitrogen equivalent, 18.1 gm., and the sum of the two is substracted from the total nonprotein nitrogen, the difference represents the excretion of nitrogen derived from actual protein catabolism. Or, $430.3 - (18.1 + 12.2) = 400$ gm. of nitrogen catabolized in sixty-four days, or $\frac{400.1}{64} = 6.3$ gm. of nitrogen a day. This is equivalent to 6.3×6.25 gm. of protein a day, or $\frac{39.4}{64.5} = 0.61$ gm. of protein per kilogram per day.

A considerable amount of space has been devoted to the explanation of the calculations of this period in order to make the processes clear to the reader. The same methods have been employed in subsequent calculations. The summarized results appear in Table 2. Of course, these methods of correction are subject to a considerable error that cannot be evaluated. The conclusions drawn from the work would not be qualitatively altered if all corrections had been omitted. The corrections are in the right direction and the fact that the application of such corrections does not significantly affect the conclusions gives the latter a validity that they would otherwise lack.

These average figures do not represent the actual course of the metabolism while the patient was in the hospital nor do they give any idea of the effects of the various therapeutic measures employed. For purposes of further analysis his course has been divided into three periods, during each of which he received a different diet. The first of these lasted from October 16 to 23, inclusive. During these eight days he was given about 50 gm. of protein, 2,250 calories and 2,000 c.c. of fluid daily, with a minimum amount of salt.

TABLE 2.—*Summary of Case 1*

Period	Number of Days	Dates, Inclusive	Calories per Day	Calories, per Kg. per Day	Nitrogen Intake, Gm.	Protein, per Kg. per Day, Gm.	Available Food Nitrogen, Gm.	Urinary Nitrogen, Gm.	Total Nitrogen Balance: As Nitrogen, Gm.	Total Nitrogen Balance: As Protein, Gm. per Day	Urinary Nonprotein Nitrogen, Gm.	Nitrogen Catabolism, Gm.	Protein Catabolism per Kg., Gm. per Day	Protein Lost as Albuminuria, Gm. per Day
1	8	Oct. 16 to 23	2,260	35	65.7	0.80	59.1	75.1	—16.0	—12.0	57.1	51.3	0.62	14.0
2	26	Oct. 16 to Nov. 18	2,600	40	327.5	1.14	309.4	224.4	34.2	8.2	200.1	188.3	0.70	15.0
3	30	Nov. 18 to Dec. 18	3,290	51	299.1	0.96	269.2	230.8	38.4	8.0	173.1	162.9	0.53	12.0
Total	64	Oct. 16 to Dec. 18	.....	..	670.2	1.07	605.0	550.4	54.6	5.3	430.3	402.6	0.61	13.5

During the second period of twenty-six days, October 24 to November 19, inclusive, he received about 75 gm. of protein and 2,600 calories. During the greater part of this period he was given an additional 5 gm. of salt daily, and from November 13 to 18 he received ammonium chlorid.

During the last period of thirty days, from November 19 to December 18, inclusive, he was given about 60 gm. of protein and 3,500 calories.

In the first period he received 65.7 gm. of nitrogen in the food, or $\frac{65.7 \times 6.25}{8}$ $= 51.3$ gm. of protein a day, or $\frac{51.3}{64.5} = 0.8$ gm. of protein per kilogram a day, and 2,260 calories per day, or $\frac{2260}{64.5} = 35$ calories per kilogram a day. Subtracting for loss in stools 10 per cent. of the food nitrogen, the available nitrogen in food becomes $0.9 \times 65.7 = 59.1$ gm. The urinary excretion at the same time was 75.1 gm., giving a negative balance of -16 gm., or 2 gm. a day, the equivalent of $2 \times 6.25 = 12.5$ gm. of protein. During the same period he excreted 112 gm. of protein, or 14 gm. a day in the urine as albumin. The nonprotein nitrogen excretion was 57.1 gm. This must be corrected for a weight loss of $71.8 - 66.8 = 5$ kg. and a reduction of blood nonprotein nitrogen from 43 to 35 mg. per cent. The correction amounts to $(64.5 \times 0.7)\ (0.43 - 0.35) + 0.9\ [0.43\ (71.8 - 64.5) - 0.35\ (66.8 - 64.5)] = 5.8$ gm. The actual nitrogen catabolism, therefore, amounted to $57.1 - 5.8 = 51.3$ gm. This is equivalent to $\frac{51.3 \times 6.25}{8} = 40.1$ gm. of protein a day, or $\frac{40.1}{64.5} = 0.62$ gm. of protein per kilogram a day.

It is therefore evident that the administration of 0.8 gm. of protein and 35 calories per kilogram a day did not suffice to prevent this patient from wasting his own body proteins. At the same time the failure to attain equilibrium on this diet was due neither to an unduly high rate of metabolism nor to a toxic destruction of protein. The diet provided quite amply for the ordinary metabolic requirements, which amounted to less than the average two-thirds gram per kilogram. The surplus of protein, however, was insufficient to cover the protein lost as albumin in the urine.

During the second period he received in his diet and as ammonium chlorid 327.5 gm. of nitrogen. Corrected for 18.1 gm. of ammonium chlorid nitrogen this becomes $327.5 - 18.1 = 309.4$ gm., or $\frac{309.4 \times 6.25}{26} = 74.4$ gm. of protein a day, or 1.14 gm. of protein per kilogram a day. After correction for nitrogen lost in the stools, the available protein nitrogen of the food comes to $0.9 \times 309.4 = 278.6$ gm. The urinary nitrogen excretion, also corrected for ammonium chlorid amounted to $262.5 - 18.1 = 244.4$ gm., leaving a positive nitrogen balance of 34.2 gm., or $\frac{34.2 \times 6.25}{26} = 8.2$ gm. of protein a day. The protein lost as albumin during the same period amounted to 389.9 gm., or 15 gm. a day. The urinary nonprotein nitrogen output was 200.1 gm. This must be corrected for 18.1 gm. of ammonium chlorid nitrogen, an increase of 1.4 kilograms of body weight and a rise of blood nonprotein nitrogen from 35 to 47 mg. per cent. The correction for rise of blood nitrogen and gain of weight equals $(64.5 \times 0.7)\ (0.47 - 0.35) + 0.9\ [0.47\ (68.2 - 64.5) - 0.35\ (66.8 - 64.5)] = 6.3$ gm. The true catabolic nitrogen, therefore, equals $200.1 - 18.1 + 6.3 = 188.3$ gm. This is equivalent to $\frac{188 \times 6.25}{26} = 45.3$ gm. of protein a day, or 0.7 gm. of protein per kilogram a day.

At first sight it appears that the administration of a larger excess of protein has, in this case, effectually prevented protein wastage, but only by increasing the protein catabolism and causing the edema and the

blood nonprotein nitrogen to increase. This was the point of view which was taken at the time and which led to reduction of the diet in the third period. In retrospect such an explanation appears less satisfactory. Throughout the whole of the first two periods the patient had profuse night sweats and occasional bouts of fever. These became more serious during the second period and were associated with attacks of lumbar pain and gross hematuria. These symptoms were probably evidences of an exacerbation of the disease which might have occurred whether the diet had been altered or not. The course of his illness was throughout marked by such attacks.

During the last period, the nitrogen intake amounted to 299.1 gm., or $\frac{299.1 \times 6.25}{30} = 62.3$ gm. of protein a day, or $\frac{62.3}{64.5} = 0.96$ gm. of protein per kilogram a day and 3,290 calories a day, or 51 calories per kilogram a day. The nitrogen intake, corrected for loss in stools, was $0.9 \times 299.1 = 269.2$ gm. The urinary nitrogen excretion came to 230.8 gm., leaving a positive balance of 38.4 gm., or $\frac{38.4}{30} = 1.28$ gm. of nitrogen a day, the equivalent of 8 gm. of protein. The protein lost as albumin during the same period amounted to 360.6 gm., or $\frac{360.6}{30} = 12$ gm. a day. The urinary nonprotein nitrogen output was 173.1 gm. The weight fell to 3.7 kg. and the blood nonprotein nitrogen diminished from 47 to 28 mg. per cent. The correction for fall of weight and blood nonprotein nitrogen amounted to $(64.5 \times 0.7)\ (0.47 - 0.28) + (68.2 - 64.5)\ (0.9 \times 0.47) = 10.2$ gm. The true catabolic nitrogen, therefore, equaled $173.1 - 10.2 = 162.9$ gm., the equivalent of $\frac{162.9 \times 6.25}{30} = 33.9$ gm. of protein a day, or 0.53 gm. per kilogram a day.

In the last period, then, by the administration of about a gram of protein per kilogram and a comparatively high caloric diet the patient was enabled to maintain a low level of nitrogen metabolism, to replace protein lost as albumin in the urine at the rate of 12 gm. a day, and to restore the depleted tissues of the body at the rate of 8 gm. or more of protein a day. It is not at all improbable that the lower protein of the first period would have resulted in the attainment of nitrogen equilibrium if it had been supported by more carbohydrate and fat calories. On the other hand, it is quite as possible that the higher protein metabolism of the earlier part of the course had no relation to the diet, but was an expression of a more serious clinical condition. It is worthy of special note that the level of blood nonprotein nitrogen varied in general with the rate of nitrogen metabolism.

One further point requires consideration. When the patient was admitted, he appeared comparatively well nourished. As the edema disappeared it became evident that his well fed look was entirely specious and that the real man beneath the edema was quite cachectic. It is surprising how much food he required to cause any healthy gain of weight in spite of the fact that his metabolism was normal. How much of his cachexia was attributable to previous misdirected diet and how much to the inherent character of the disease it is impossible to

say. The fact that he was able to store so much protein for so considerable a time is itself convincing evidence that there had been previous protein starvation. If it is assumed that protein makes up as much as 25 per cent. of muscle tissue the amount of protein retained in the sixty-four days in the hospital represents $\frac{341}{0.25} = 1{,}364$ gm. of muscle tissue. This gain, of course, masks to a certain extent the effects of diuresis, which must have been greater than the observed weight loss would indicate.

Case 2.—A Polish rubber worker, aged 43, married, was admitted to the hospital, Jan. 10, 1925, complaining especially of swelling of the abdomen. Aug. 29, 1924, he developed a coryza and sore throat that kept him in bed for two weeks. When he returned to work he noticed that his face, legs, genitals and abdomen, and especially the last, became swollen. This subsided after rest in bed, only to return as soon as he resumed his normal activities. He noticed at the same time that he was more comfortable sitting up or reclining on two pillows than he was in the recumbent position, although he was not noticeably short of breath. About the beginning of November he went to another hospital; the edema disappeared rapidly after rest and medication. He was discharged after twelve days. As soon as he left the hospital, edema, slight orthopnea and weakness recurred. At no time did he notice hematuria, dysuria or nocturia; but he had been troubled somewhat with diurnal frequency

On admission he appeared somewhat pale and sallow, but large, well developed and fairly well nourished. His face was somewhat puffy. His pharynx and tonsils were injected and red, but there were no evidences of an acute inflammatory process. Over the bases of both lungs there were dulness, diminished breath sounds and râles, extending somewhat higher on the right side than on the left. The heart was not enlarged and presented no significant abnormalities; the systolic blood pressure was 122, the diastolic 78. The pulse was regular, of good quality and quite slow (50 per minute); respirations were quiet and normal in rate and rhythm. The abdomen was distended, with signs of considerable ascites. The genitals were markedly swollen and there was slight pitting edema of the backs of the legs and thighs and over the sacrum. Otherwise physical examination revealed no abnormalities. Ophthalmoscopic examination showed no signs of retinitis or vascular disease.

The blood Wassermann reaction was negative. Roentgen-ray examination of the chest showed no cardiac enlargement and no signs of pulmonary disease. Phenolsulphonephthalein excretion, January 11, was 32 per cent. in two hours and ten minutes. An electrocardiogram, January 14, showed no abnormalities.

He was given a salt poor diet containing about 60 gm. of protein and 2,500 calories with fluids limited to 1,500 c.c. On this regimen he lost little weight, so he was given a course of ammonium chlorid. This resulted in some diuresis, but at the end of the treatment he complained of pain and tenderness in the lumbar region on both sides and ran a temperature for two days (100.4 F., January 23, and 102.6 January 24).

The urine was cultured, January 20 and again January 26. On both occasions every specimen contained a gram-negative, nonmotile bacillus that produced no acid on most sugars. This organism was not agglutinated by the patient's serum. February 11, the phenolsulphonephthalein excretion was 40 per cent. in two hours and ten minutes.

After the first course of ammonium chlorid diuresis continued for two or three days and then ceased. He was therefore given another course, beginning January 29. This was less effective than the first. It was, however, followed by a period of gradually diminishing weight.

February 14, another course of ammonium chlorid was started without effect. From time to time after this he was given urea with little noticeable effect. All obvious edema was gone; but there was some swelling of the feet after he had been up and about for a while.

Roentgen-ray examination of the kidneys, March 13, revealed no evidences of enlargement or calculus formation.

March 17, tonsillectomy was performed under local anesthesia. In the next three days he lost 2 kg. of weight, which caused the disappearance of the last vestiges of edema. After this his general condition improved steadily.

Blood counts showed a low grade anemia. On admission there were 4.5 million red cells and about 100 per cent. of hemoglobin. On discharge, in spite of his improvement, the red cells had fallen to 3.4 million, and the hemoglobin to 85 per cent. (Haldane scale).

The urine on admission contained many casts and red blood cells and moderate numbers of leukocytes. Occasionally it appeared grossly bloody. The cells diminished in numbers as the patient improved and after the middle of March all signs of hematuria had disappeared.

Beside the febrile attack noted above, the temperature rose to 100.4 F., March 5. On both occasions he complained of slight sore throat and both times showed slight exacerbations of the hematuria.

The detailed metabolism data appear in Table 3 and are summarized in Table 4.

During the whole time he was studied in the hospital, ninety-two days, he received a total of 1,091.7 gm. of nitrogen. Of this 34.3 gm. was given as ammonium chlorid and 46.7 gm. as urea. The actual amount of food nitrogen given was therefore $1{,}091.7 - (34.3 + 46.7) = 1{,}010.7$ gm., or $\frac{1{,}010.7 \times 6.25}{92} = 68.7$ gm. of protein a day, or $\frac{68.7}{64.6} = 1.06$ gm. per kilogram a day.

In order to find out whether the large positive nitrogen balance he exhibited could be attributed to an excess of nitrogen in the stools, the stools were analyzed for two separate four-day periods during the last two weeks of his stay in the hospital, and were found on both occasions to contain 1.9 gm. of nitrogen a day. At that time he was receiving 12.5 gm. of nitrogen a day in his food. He was therefore losing about 15 per cent. of this food nitrogen instead of the usual 10. Whether he lost as much earlier in the course of his disease it is impossible to say; but it is unlikely that he lost more. For the purpose of calculation it will be assumed that 1.9 gm. of nitrogen were excreted in the stools daily throughout the course of study. The actual available food nitrogen then becomes $1{,}010.7 - (92 \times 1.9) = 835.9$ gm.

The nitrogen output amounted to 723.6. If this also is corrected for ammonium chlorid and urea, it becomes $723.6 - (34.3 \times 46.7) = 640.5$ gm., which leaves a positive nitrogen balance of 195.4 gm., the equivalent of $\frac{195.4 \times 6.25}{92} = 13.3$ gm. of protein a day. During the same period he excreted in the urine, as albumin, 962.5 gm. of protein, or 10.4 gm. a day. The nonprotein nitrogen output came to 572.1 gm., of which again 34.3 and 46.7 gm. were derived from ammonium chlorid and urea, respectively. The blood nonprotein nitrogen fell from 61 to 30 mg. per cent., and the body weight from 76.4 to 64.6 kg. The latter accounted for $(64.6 \times 0.7)\ (0.61 - 0.30) + (76.4 - 64.6)\ (0.9 \times 0.61) = 20.5$ gm. The actual catabolic nitrogen, therefore, amounted to $572.1 - (34.3 + 46.7 + 20.5) = 470.6$ gm., or $\frac{470.6 \times 6.25}{92} = 32$ gm. of protein a day, or 0.5 gm. of protein per kilogram a day.

The average level of protein metabolism in this case is surprisingly low, much lower than that of the first patient. The latter, however, had more continuous evidences of infection and received a lower caloric diet throughout.

TABLE 3.—*Data in Case 2*

Date	Food, Calories	Fluids: Intake, C.c.	Fluids: Urine, C.c.	Fluids: Balance, C.c.	Weight, Kg.	Total Nitrogen: Intake, Gm.	Total Nitrogen: Urine, Gm.	Total Nitrogen: Balance, Gm.	Urine Non-protein Nitrogen, Gm.	Protein Lost as Albumin, Gm.	Chlorid as Sodium Chlorid: Intake, Gm.	Chlorid as Sodium Chlorid: Output, Gm.	Chlorid as Sodium Chlorid: Balance, Gm.	Blood Nonprotein Nitrogen, Mg. per 100 C.c.	Plasma Protein, per Cent.	Special Medication
Jan. 12	2,542	770	1,040	—270	76.4	9.82	8.57	—1.25	7.36	7.6	1.25	3.27	—2.02	61	4.03	
13	2,554	1,000	690	310	77.3	9.91	6.00	3.91	4.86	7.1	1.01	2.51	—1.50	..	....	
14	2,542	1,230	1,060	170	76.2	9.82	8.82	1.00	7.13	10.6	1.25	3.54	—2.29	..	....	
15	2,542	1,160	1,200	—40	76.6	9.82	8.98	0.84	7.38	10.0	1.25	4.30	—3.05	..	....	
16	2,496	1,545	880	665	76.8	9.70	6.49	3.21	4.80	10.6	1.23	3.04	—1.81	..	....	
17	2,542	1,470	1,285	185	76.8	9.82	8.76	1.06	7.17	9.9	1.25	4.18	—2.93	..	....	
18	2,596	1,250	980	270	75.5	10.05	7.23	2.82	5.66	9.8	1.90	3.40	—1.50	..	....	
19	2,542	1,930	1,370	560	75.7	9.82	9.16	0.66	7.08	13.0	1.25	4.80	—3.55	..	....	
20	2,542	1,900	1,240	360	75.0	13.75	7.33	6.42	6.00	8.3	17.65	4.46	13.19	41	4.12	Ammonium chlorid, 15 gm.
21	2,476	1,495	1,440	55	74.3	13.43	9.27	4.16	7.16	13.2	17.23	6.46	10.77	..	....	Ammonium chlorid, 15 gm.
22	2,542	1,705	2,020	—315	73.9	13.75	14.50	—0.45	11.70	15.6	17.65	10.02	7.63	..	....	Ammonium chlorid, 15 gm.
23	2,475	1,450	1,780	—330	72.7	9.16	10.68	—1.52	7.97	16.9	1.85	10.47	—8.62	45	4.20	
24	2,542	1,470	1,360	110	72.3	9.82	9.79	0.03	6.81	18.6	1.25	7.94	—6.69	..	....	
25	2,326	1,470	1,190	280	71.6	8.64	8.45	0.19	6.24	13.2	0.77	6.16	—5.39	..	....	
26	2,486	1,325	980	345	71.2	9.55	5.86	3.69	4.70	7.3	1.13	4.02	—2.89	..	....	
27	2,534	1,225	1,120	105	71.2	9.75	6.71	3.04	5.81	5.6	1.20	4.66	—3.46	..	....	
28	3,284	1,765	1,020	745	70.6	9.92	5.98	3.94	5.11	5.4	1.10	4.14	—3.04	..	....	
29	3,265	1,445	1,100	345	70.5	12.42	6.38	6.04	5.02	8.0	11.67	4.25	7.42	..	....	Ammonium chlorid, 10 gm.
30	3,267	1,405	2,330	—925	70.0	12.37	13.51	—1.14	10.88	16.4	12.61	10.76	1.85	..	....	Ammonium chlorid, 10 gm.
31	3,217	1,455	980	575	70.5	10.93	6.50	4.43	5.02	9.3	6.48	5.24	1.24	..	....	Ammonium chlorid, 5 gm.
Feb. 1	2,542	1,280	1,250	30	70.1	11.14	7.40	6.74	5.78	10.2	6.72	6.05	1.67	..	....	Ammonium chlorid, 5 gm.
2	2,542	1,480	1,840	—640	70.4	11.14	9.92	1.22	7.67	14.1	6.72	9.80	—3.08	..	....	Ammonium chlorid, 5 gm.
3	3,148	1,450	1,220	230	69.7	11.35	7.08	4.27	5.09	12.4	6.75	6.39	0.36	..	....	Ammonium chlorid, 5 gm.
4	3,091	1,545	1,380	165	69.7	11.03	9.02	2.01	6.31	16.9	6.61	6.51	0.10	..	....	
5	3,056	1,865	1,220	645	69.5	9.11	7.78	1.33	6.10	10.5	0.81	5.98	—5.17	..	....	
6	3,153	1,485	1,110	375	69.2	10.08	8.42	1.66	6.98	9.0	1.37	4.71	—3.34	..	....	
7	3,160	1,435	1,145	290	68.8	10.29	8.96	1.33	7.22	10.3	1.03	5.45	—4.42	..	....	
8	3,190	1,340	1,474	—134	68.6	12.14	8.94	3.20	7.18	11.0	0.95	5.84	—4.89	..	....	Urea, 5 gm.
9	3,319	1,455	1,100	355	68.5	12.44	7.44	5.00	6.00	9.0	1.58	3.98	2.40	..	....	Urea, 5 gm.
10	3,201	1,440	1,090	350	68.3	10.30	7.18	3.12	5.86	8.3	1.37	3.88	—2.51	..	....	
11	3,169	1,105	1,355	—250	68.2	10.29	7.54	2.75	6.03	9.4	1.03	4.04	—3.01	..	....	
12	3,194	1,495	900	595	68.3	10.00	6.17	3.83	5.15	6.4	1.22	2.86	—1.64	..	....	
13	3,201	1,665	1,100	565	68.6	12.92	7.28	5.64	6.14	7.1	12.30	3.85	8.45	45	3.95	Ammonium chlorid, 10 gm.
14	3,288	1,615	1,350	265	68.9	13.02	8.82	4.20	6.91	11.9	12.31	5.35	6.96	..	....	Ammonium chlorid, 10 gm.
15	3,162	1,465	1,145	320	68.6	11.33	7.58	3.75	5.98	10.0	7.47	5.47	2.00	..	....	Ammonium chlorid, 6 gm.
16	3,319	1,655	1,100	555	68.8	11.68	7.77	3.91	5.98	11.2	8.14	5.50	2.64	..	....	Ammonium chlorid, 6 gm.
17	3,100	1,825	1,100	725	69.1	11.40	7.58	3.82	5.80	11.1	7.88	5.30	2.58	..	....	Ammonium chlorid, 6 gm.
18	3,114	1,435	1,720	—285	68.4	10.79	9.68	1.11	7.48	13.7	4.29	8.36	—4.07	..	....	Ammonium chlorid, 3 gm.
19	3,175	1,935	1,170	765	68.9	9.42	6.63	2.79	5.12	9.4	1.54	5.76	—4.22	..	....	
20	3,201	1,940	1,295	645	68.8	12.63	7.53	5.10	5.97	9.8	1.37	5.80	—4.43	..	....	Urea, 5 gm.
21	3,288	1,965	1,230	735	68.8	10.40	7.78	2.62	6.08	10.6	1.38	5.36	—3.98	..	....	
22	3,309	1,955	1,260	695	69.0	10.05	7.61	2.44	5.85	11.0	1.54	5.24	—3.70	..	....	
23	3,175	1,975	1,100	875	69.0	9.42	7.15	2.27	5.50	10.3	1.54	4.66	—3.12	..	....	
24	3,190	1,740	1,330	410	69.1	9.81	7.54	2.27	6.18	8.5	0.95	5.43	—4.48	..	....	

	25	3,402	1,650	1,380	270	69.2	11.60	7.54	4.06	6.04	9.4	1.95	4.97	—3.02	..	....	Urea, 10 gm.
	26	3,570	2,045	2,360	—315	69.4	16.81	13.07	3.74	11.37	10.6	1.79	8.97	—7.18	..	....	Urea, 10 gm.
	27	3,646	1,710	1,700	10	69.3	16.67	10.30	6.37	8.22	13.0	1.64	6.19	—4.55	..	....	
	28	3,570	1,928	1,000	928	69.4	12.14	6.81	5.33	5.26	19.7	1.79	3.50	—1.71	..	....	
March	1	3,640	1,308	1,520	—212	69.3	12.24	9.12	3.12	6.94	13.5	1.46	5.23	—3.77	..	....	
	2	3,570	1,465	1,390	75	69.8	16.81	9.49	7.32	7.47	12.6	1.79	5.40	—3.61	..	....	Urea, 10 gm.
	3	3,646	1,835	1,080	755	70.0	12.00	8.08	3.92	6.40	10.5	1.64	4.41	—2.77	34	4.20	
	4	3,530	1,095	910	185	69.5	12.16	7.08	5.08	5.50	9.8	1.61	4.00	—2.39	..	....	
	5	3,570	1,498	810	688	69.0	12.14	7.28	4.86	5.50	11.1	1.79	3.38	—1.59	..	....	
	6	3,426	2,000	1,270	730	69.5	15.71	9.49	6.22	7.82	10.4	0.88	4.67	—3.79	..	....	Urea, 10 gm.
	7	3,523	2,245	1,420	825	68.4	16.62	10.86	5.76	9.26	10.0	1.75	5.57	—3.82	..	....	Urea, 10 gm.
	8	3,646	2,135	1,450	685	68.2	16.67	10.19	6.48	9.04	7.2	1.64	4.93	—3.29	..	....	Urea, 10 gm.
	9	3,345	1,728	1,230	498	68.2	16.67	10.13	6.54	8.93	7.5	1.75	4.35	—2.60	..	....	Urea, 10 gm.
	10	3,447	1,988	1,350	638	67.9	11.34	9.66	1.68	8.00	10.4	1.41	5.40	—3.99	..	....	
	11	3,473	1,990	910	1,080	67.7	12.78	6.90	5.88	5.57	8.3	1.68	3.86	—2.18	..	....	
	12	3,438	1,995	1,080	915	67.6	11.52	6.84	4.68	5.18	10.4	1.31	4.54	—3.23	..	....	
	13	3,473	1,990	1,160	830	67.7	12.78	6.90	5.88	5.15	10.9	1.68	4.64	—2.96	..	....	
	14	3,602	1,925	1,600	325	67.5	12.35	7.10	5.25	5.25	11.6	1.77	5.06	—3.80	..	....	
	15	3,570	1,978	1,770	208	67.5	12.14	7.40	4.74	5.29	6.9	1.79	6.44	—4.65	..	....	
	16	3,640	2,108	1,660	448	66.8	12.24	6.96	5.28	5.06	11.9	1.46	5.55	—4.09	..	....	
	17	.....	900	850	50	66.1	....	5.61	—5.61	3.63	12.4	....	5.54	—5.54	.	....	Operation
	18	3,473	2,000	1,240	760	65.2	12.78	7.76	5.02	6.42	11.9	1.68	5.83	—4.15	..	....	
	19	3,570	2,030	1,230	800	64.8	12.14	6.51	5.63	5.12	11.5	1.79	4.43	—2.64	..	....	
	20	3,473	2,465	1,150	1,315	64.8	12.78	6.06	6.72	4.60	9.1	1.68	4.60	—2.92	..	....	
	21	3,646	2,095	1,065	1,030	64.7	12.00	5.89	6.11	4.50	8.7	1.64	4.07	—2.41	..	....	
	22	3,602	2,050	1,265	785	64.7	12.35	6.41	5.94	4.99	8.9	1.78	4.86	—3.08	..	....	
	23	3,640	2,090	1,490	600	64.8	12.24	6.91	5.33	5.47	8.4	1.46	5.13	—3.67	.	....	
	24	3,626	2,000	1,620	380	64.0	12.17	6.26	5.91	4.87	8.7	1.86	4.92	—3.06	..	....	
	25	3,514	2,045	1,420	625	64.0	12.16	6.32	5.84	4.77	9.7	1.65	4.23	—2.58	..	....	
	26	3,473	2,050	1,660	390	63.9	12.78	7.26	5.52	5.49	12.3	1.68	5.54	—3.86	..	....	
	27	3,473	1,795	1,210	585	63.8	12.78	5.63	7.15	4.20	7.7	3.68	4.16	—0.48	..	....	
	28	3,130	2,300	1,590	610	64.1	12.12	5.89	6.23	4.48	8.8	3.43	3.91	—0.48	..	....	
	29	3,602	1,890	1,740	150	63.6	12.35	6.52	5.83	5.05	9.2	3.77	4.46	—0.69	..	....	
	30	3,646	2,035	1,650	385	74.0	12.00	6.85	5.15	5.28	9.8	3.46	4.49	—0.85	..	....	
	31	3,640	1,900	1,650	250	64.1	12.24	6.36	5.88	4.80	9.8	3.46	4.13	—0.67	..	....	
April	1	3,473	1,890	1,900	—10	63.9	12.78	7.32	5.46	5.74	9.9	3.68	6.00	—2.32	..	....	
	2	3,570	1,765	1,260	505	63.9	12.14	5.10	7.04	4.10	6.3	3.79	3.40	0.39	..	....	
	3	3,575	1,960	1,760	200	64.5	12.25	6.50	5.75	5.14	8.5	3.66	4.33	—0.67	..	....	
	4	3,556	2,130	1,390	740	64.2	12.17	5.28	6.89	4.34	12.1	3.71	3.95	—0.24	..	....	
	5	3,626	2,105	1,860	245	65.0	12.17	6.58	5.59	5.30	8.0	3.86	4.95	—1.09	..	....	
	6	3,640	1,950	2,010	—60	64.4	12.24	7.12	5.12	5.70	8.9	3.46	5.47	—2.01	..	....	
	7	3,646	1,935	2,050	—115	64.3	12.00	7.91	4.09	6.27	10.9	3.64	5.74	—2.10	..	....	
	8	3,473	1,790	1,270	520	64.8	12.78	6.31	6.47	4.95	8.5	3.68	4.62	—0.94	.	....	
	9	3,570	2,345	1,560	785	64.8	12.14	6.30	5.84	4.93	8.6	3.79	4.84	—1.05	..	....	
	10	3,438	1,920	1,910	10	64.8	11.52	6.92	4.60	5.56	8.5	3.31	5.63	—2.32	..	....	
	11	3,602	2,075	2,000	75	65.1	12.35	7.70	4.65	6.08	10.1	3.77	6.60	—2.83	..	....	
	12	3,626	1,915	1,540	375	65.7	12.17	8.24	3.93	6.64	10.0	3.86	5.82	—1.96	..	....	
	13	3,640	2,150	2,150	0	64.9	12.24	10.38	1.86	8.66	10.8	3.46	6.75	—3.29	..	....	
	14	3,646	2,090	1,720	370	64.6	12.00	7.00	5.00	5.42	9.9	3.64	3.65	—0.01	30	4.34	

The course of this case has again been divided into periods corresponding to different diets. The effect of ammonium chlorid and urea have been reserved for subsequent discussion and may be neglected for the present.

The first period of seventeen days, from January 12 to 28, inclusive, he received about 60 gm. of protein and 2,500 calories daily, with 1,500 c.c. of fluid and minimum salt. During the second period of twenty-seven days, from January 29 to February 24, inclusive, the protein remained unchanged, but he was given additional fat and carbohydrate to make 3,150 calories. The third period of twenty days, February 25 to March 16, inclusive, he received 75 gm. of protein and 3,530 calories and was allowed 2,000 c.c. of fluid. During the last period of twenty-six days, March 20 to April 15, inclusive, he continued the same dietary regimen. Three days have been omitted between the third and fourth periods. The first of these is the day on which tonsillectomy was performed. The metabolism of these periods and the totals for the whole study appear in Table 4.

The nitrogen intake during the first period of seventeen days was 176.5 gm., of which 11.8 gm. was derived from ammonium chlorid, leaving a total food nitrogen of 164.7 gm. or $\frac{164.7 \times 6.25}{17} = 60.6$ gm. of protein a day, or 0.94 gm. per kilogram a day. If $(1.9 \times 17) = 32.3$ gm. is subtracted for loss in stools, the available food nitrogen becomes 132.3 gm. The nitrogen output in the urine = 143.3 gm., which must also be diminished by 11.8 gm. as ammonium chlorid, leaving 130.5 gm. and making a total positive nitrogen balance of 1.8 gm., or $\frac{1.8 \times 6.25}{17}$ = 0.66 gm. of protein a day. At the same time he lost as albumin in the urine 182.7 gm. of protein, or 10.75 gm. a day. The nonprotein nitrogen output was 113 gm., of which 11.8 gm. was derived from ammonium chlorid and (64.6×0.7) $(0.61 - 0.45) + 0.9$ $[0.61$ $(76.4 - 64.6)$ $- 0.45$ $(70.6 - 64.6)]$ = 11.3 gm. is accounted for by reduction of blood nonprotein nitrogen from 61 to 45 mg. per cent. and a change of weight from 76.4 to 70.6 kg. The nitrogen actually catabolized, therefore, amounts to $113 - (11.8 + 11.3)$ = 89.9 gm., which is equivalent to $\frac{89.9 \times 6.25}{17}$ = 33 gm. of protein a day, or $\frac{33}{64.6}$ = 0.51 gm. of protein per kilogram a day.

By the administration of 0.94 gm. of protein per kilogram a day and 2,500 calories, then, it was just possible to maintain nitrogen equilibrium in the face of an albuminuria equivalent to 10.75 gm. of protein a day, and this end was only attained by virtue of the fact that the nitrogen metabolism maintained a level below the normal average.

During the second period of twenty-seven days, he received 297.9. gm. of nitrogen, of which 22.5 gm. was given as ammonium chlorid and 7 gm. as urea. If this is subtracted from the intake it leaves $297.9 - (22.5 + 7)$ = 268.4 gm., the equivalent of $\frac{268.4 \times 6.25}{27}$ = 62.2 gm. of protein a day or $\frac{62.2}{64.6}$ = 0.96 gm. per kilogram a day, approximately what he received during the first period. However, he got 3,150 calories a day instead of the earlier 2,500.

If the nitrogen lost in the stools is subtracted from the food nitrogen, the available nitrogen comes to $268.4 - (27 \times 1.9)$ = 217 gm. The urinary nitrogen excretion, corrected for ammonium chlorid and urea = $215.2 - (22.5 + 7)$ = 185.7 gm., leaving a positive nitrogen balance of 32.3 gm., the equivalent of $\frac{32.3 \times 6.25}{27}$ = 7.5 gm. of protein a day. During the same time his albuminuria alone accounted for 286.2 gm. of protein, or 10.6 gm. a day. The nonprotein nitrogen output was 169.3. This must be corrected for ammonium chlorid, urea and change of weight from 70.6 to 69.1 kg. The blood nonprotein nitrogen was not estimated at the end of the period, but must have remained relatively constant because it was 45 mg. per cent. on both January 23 and February 13.

TABLE 4.—*Summary in Case 2*

Period	Number of Days	Dates, Inclusive	Calories per Day	Calories, per Kg. per Day	Nitrogen Intake, Gm.	Protein, per Kg. per Day, Gm.	Available Food Nitrogen, Gm.	Urinary Nitrogen, Gm.	Total Nitrogen Balance		Urinary Nonprotein Nitrogen, Gm.	Nitrogen Catabolism, Gm.	Protein Catabolism per Kg., Gm. per Day	Protein Lost as Albuminuria, Gm. per Day
									As Nitrogen, Gm.	As Protein, Gm. per Day				
1	17	Jan. 12 to Jan. 28	2,500	39	176.5	0.94	132.3	130.5	1.8	0.7	113.0	89.9	0.51	10.8
2	27	Jan. 29 to Feb. 24	3,150	49	297.9	0.96	217.0	185.7	32.3	7.5	169.3	133.7	0.48	10.6
3	20	Feb. 25 to Mar. 16	3,530	55	273.4	1.21	211.4	147.2	64.2	20.0	137.3	107.2	0.52	10.8
4	26	Mar. 20 to Apr. 15	3,530	55	318.9	1.19	269.5	175.0	94.5	22.7	137.3	135.4	0.50	9.3
Total	92	Jan. 12 to Apr. 15	.....	..	1,091.7	1.06	835.0	640.5	194.5	13.2	572.1	470.6	0.50	10.4

The loss of nonprotein nitrogen due to loss of body weight is equal to $(70.6 - 69.1)\ (0.9 \times 0.45) = 6.1$ gm. The actual nitrogen catabolism, therefore, amounted to $169.3 - (22.5 + 7.0 + 6.1) = 133.7$ gm., which represents $\frac{133.7 \times 6.25}{27} = 31$ gm. of protein a day or $\frac{31}{64.6} = 0.48$ gm. per kilogram a day.

It is therefore evident that by the addition of extra fat and calories it was possible to reduce the nitrogen metabolism and to increase the storage of protein in spite of the fact that the albuminuria remained practically constant.

During the third period of twenty days both calories and protein in the diet were increased and he was allowed as much as 2,000 c.c. of fluid a day. The total nitrogen intake amounted to 273.4 gm., of which 24 gm. was given as urea. The actual food nitrogen was therefore $273.4 - 24 = 249.4$ gm., the equivalent of $\frac{249.4 \times 6.25}{20} = 77.9$ gm. of protein a day, or $\frac{77.9}{64.6}$, or 1.21 gm. per kilogram a day. After correction for loss in stools the available food nitrogen becomes $249.4 - (20 \times 1.9) = 211.4$ gm. The urinary nitrogen corrected for administered urea $= 171.2 - 24 = 147.2$ gm., leaving a positive balance of 64.2 gm., equivalent to $\frac{64.2 \times 6.25}{20} = 20$ gm. of protein a day. The protein lost as albumin during the same period was 215.7 gm., which represented 10.8 gm. of protein a day. The urinary nonprotein nitrogen was 137.3 gm. From this must be subtracted 24 gm. for the urea given, and because the blood nonprotein nitrogen fell from 45 to 34 mg. per cent. and the body weight from 69.1 to 66.8 kg., in addition $(64.6 \times 0.7)\ (0.45 - 0.34) + 0.9\ [0.45\ (69.1 - 64.5) - 0.34\ (66.8 - 64.6)] = 6.1$ gm. The actual nitrogen catabolism then came to $137.3 - (24.0 + 6.1) = 107.2$ gm., the equivalent of $\frac{107.2 \times 6.25}{20} = 33.5$ gm. of protein a day, or 0.52 gm. per kilogram a day.

The administration of an additional 15 gm. of protein a day, therefore, resulted in a negligible increase of protein metabolism and an increase of protein storage almost equivalent to the added food protein. Meanwhile the albuminuria remained practically unchanged.

During the last period of twenty-six days, the diet remained unchanged. Meanwhile, however, the patient's tonsils had been removed. He received altogether 318.9 gm. of nitrogen in this diet, that is, $\frac{318.9 \times 6.25}{26} = 76.6$ gm. of protein a day, or $\frac{76.6}{64.6} = 1.19$ gm. per kilogram a day. If the food nitrogen is corrected for loss in the stools, the available nitrogen becomes $318.9 - (26 \times 1.9) = 269.5$ gm. The urinary nitrogen, for the same period was 175 gm., leaving a positive balance of 94.5 gm., representing $\frac{94.5 \times 6.25}{26} = 22.7$ gm. of protein a day, a surprisingly large amount. (It must be added that the operation, which was performed under procain anesthesia, was attended by no obvious change in rate of nitrogen metabolism.) The protein lost as albumin amounted to 242.1 gm., or $\frac{242.1}{26} = 9.3$ gm. a day. The urinary nonprotein nitrogen amounted to 137.3 gm. The blood nonprotein nitrogen fell from 34 mg. per cent. and the weight from 64.8 to 64.6 kg. The actual nitrogen catabolism, therefore, amounted to $137.3\ (64.6 \times 0.7)\ (0.34 - 0.30) + (64.8 - 64.6)\ (0.9 \times 0.34) = 135.4$ gm. This is equivalent to $\frac{135.4 \times 6.25}{26} = 32.5$ gm. of protein a day, or 0.50 gm. per kilogram a day.

The degree of nitrogen storage in this period is amazing. There is no evidence that the capacity of the organism for protein is diminishing.

On the contrary, if anything, it appears to be increasing. These changes were associated with marked clinical improvement, which was reflected in a diminution of albumin and disappearance of the last vestiges of hematuria and edema.

During the last few days the body weight increased somewhat without any evidences of edema. There can be little doubt that this gain represented a restitution of healthy tissue. There could be little doubt from the appearance of the patient at the end of his diuresis that he was actually wasted.

CASE 3.—A Greek man, aged 30, was admitted to the hospital, Feb. 2, 1924. Three months earlier he noticed that his feet and legs were swollen. The swelling increased gradually for a few days, but cleared up rapidly under Turkish bath treatment. Ten days before admission, when he awoke in the morning he found that the swelling had recurred and he had considerable difficulty in getting his shoes on. The edema increased gradually but steadily, without other symptoms, so that he was forced to stop work after about four days. He again tried the effect of a Turkish bath, but this time obtained no relief from the treatment. At no time had he noticed any symptoms other than the edema. He could recall no cold or other infection that could have precipitated the nephritis and gave no history of any previous diseases of importance.

When he entered the hospital he appeared well developed and nourished. The temperature was 99 degrees F., pulse 90 and respirations 20 a minute and quite normal in character; the systolic blood pressure was 154, the diastolic 85. The eyelids were somewhat puffy and there was a marked pitting edema involving the whole trunk, the genitalia and the lower extremities. There were signs of fluid in the right pleural and the peritoneal cavities. The liver and the spleen could not be felt and did not seem to be enlarged. There were no evidences of functional or organic heart disease. There was a small amount of exudate along the retinal vessels, but no other evidences of retinal changes. The blood count showed 4,800,000 red blood cells and 9,500 leukocytes, of which 71 per cent. were polymorphonuclear neutrophils.

The blood Wassermann reaction was negative. The urine contained a large amount of albumin and casts of all kinds but no blood cells. The phenolsulphonephthalein excretion was 55 per cent. in two hours and ten minutes.

Cultures of the urine on two occasions obtained a nonhemolytic streptococcus, the first time in pure culture, the second time contaminated with *Staphylococcus albus*. He was placed on a diet containing 50 gm. of protein and 2,000 calories, with fluids limited to 1,500 c.c. per day (actually he took 1,000 c.c. or less). At the end of five days, as the edema had not diminished, the diet was made salt poor. Diuresis began at once, and by the end of four days, he had lost 8 pounds (3.6 kg.) of weight. At this time, February 10, because he was hungry, his diet was increased to 60 gm. of protein and 2,500 calories. Diuresis and loss of weight continued. The second examination of arterial blood was made before breakfast on the morning of February 14. The urine at this time contained considerable albumin and casts but no blood cells. The blood pressure had fallen to 115. Unfortunately, the urine specimens up to this time were not complete and the nitrogen, salt and water balances cannot, therefore, be calculated.

Under the same regimen he continued to lose weight for five days, although the character of the urine did not change. February 19, the addition to the diet of 3 gm. of sodium chlorid was associated with an increase of the urine volume without any rise in the chlorid excretion. The last examination of arterial blood was made before breakfast of the day he was discharged from the hospital, February 23. The edema had by this time completely disappeared,

but the character of the urine was unaltered. The basal metabolism, February 9, was +16 per cent.; February 16, it was −5 per cent. The results of the metabolism studies appear in Table 5.

The patient was unable to speak any English and it proved difficult to obtain his cooperation. For this reason the urine was lost daily throughout the earlier part of his course in the hospital. From February 14 on, with the exception of one day, complete collections were effected. This gave eight days of satisfactory study, the data for which appear in Table 5. During this period he received a salt poor diet containing about 60 gm. of protein and 2,500 calories, with a low fluid intake. Diuresis proceeded for the first three days. At the end of this time the edema had disappeared completely.

During the eight days of study he received 76.8 gm. of nitrogen in his food, representing 60 gm. of protein a day, or about 1 gm. per kilogram. Subtracting 10 per cent. for loss in the stools, the available nitrogen becomes 76.8 − 7.7 = 69.1 gm. The total urinary nitrogen amounted to 60.8 gm., leaving a positive balance of 8.3 gm., or $\frac{8.3 \times 6.25}{8} = 6.5$ gm. of protein a day. At the same time he lost as albumin in the urine from 6 to 12 gm. of protein a day. The urinary nonprotein nitrogen excretion was 23.7 gm. for the four days that it was determined. During this time the weight fell about 2 kg. and the blood nonprotein nitrogen probably less than 4 mg. per cent. Because of the uncertainty of these two changes, corrections have not been made for them. The rate of nitrogen catabolism calculated from the urinary nonprotein nitrogen amounts to $\frac{23.7 \times 6.25}{8} = 37$ gm. of protein a day, or 0.62 gm. per kilogram a day.

TABLE 5.—*Data in Case 3*

Date, Feb.	Food, Calories	Fluids			Weight, Kg.	Total Nitrogen			Urine Nonprotein Nitrogen, Gm.	Protein Lost as Albumin, Gm.	Urine Chloride as Sodium Chloride, Gm.	Blood Nonprotein Nitrogen, Mg. per 100 C.c.	Plasma Proteins, per Cent.
		Intake, C.c.	Urine, C.c.	Balance, C.c.		Intake, Gm.	Urine, Gm.	Balance, Gm.					
14	2,500	800	1,340	−540	62.0	9.6	7.7	1.9	6.1	9.4	5.6	33	4.50
15	2,500	600	.....	.....	60.9	9.6	...	...	...	...	...	..	....
16	2,500	600	630	−30	60.4	9.6	4.0	5.6	3.1	6.1	4.1	..	....
17	2,500	600	1,300	−700	60.9	9.6	9.0	0.6	7.2	11.2	6.8	..	....
18	2,500	800	1,900	−1,100	59.7	9.6	9.3	0.4	7.3	12.3	7.7	..	....
19	2,500	600	1,380	−780	59.7	9.6	6.8	2.8	...	...	5.5	..	....
20	2,500	800	1,040	−240	59.6	9.6	6.6	3.0	...	...	3.6	..	....
21	2,500	600	1,380	−780	60.3	9.6	8.3	1.4	...	...	5.4	..	....
22	2,500	650	1,380	−730	59.7	9.6	9.2	0.5	...	...	4.0	29	4.49
Total	20,000	5,450	10,350	−4,900		76.8	60.8	16.1	...	...	42.7		
Daily aver.	2,500	681	1,294	−613		9.6	7.6	2.0	5.9	9.8	5.3		

This patient again exhibited a comparatively normal rate of nitrogen catabolism and, by the administration of an excess of protein and adequate calories, was enabled to store protein in spite of a considerable albuminuria. Again this capacity for storage is an indication of previous protein starvation. Whether this was referable to an acceleration of general metabolism in the earlier stages of the disease or to a more profuse albuminuria or to insufficient diet can only be conjectured. While he was in the hospital, the basal metabolism fell from +16 per cent. to −5 per cent. Unfortunately urinary studies of the earlier period are lacking.

CASE 4.—A Polish man, aged 33, was first seen as an outpatient, Feb. 8, 1924. One year before this, without any obvious cause, he developed puffiness of the ankles and occasional headaches. Two months' rest in bed resulted in no improvement. The edema varied somewhat in extent and severity, but never disappeared entirely. After about six months he began to have frequent attacks of severe headache, associated with vomiting. He had to urinate frequently during the day and during the night, but passed only small amounts at each voiding. From the onset he was troubled with excessive weakness and lassitude. He had no dyspnea, palpitation, precordial pain nor visual disturbances. Except that he had had rheumatism in 1916 and again in 1918, the past history was unimportant.

When he was first seen he weighed 79.7 kg. He appeared quite pale; his face was puffy, and there was moderate pitting edema of the legs. Respirations were quite normal. The heart was somewhat enlarged to the left and there was a faint systolic murmur at the apex. The systolic blood pressure was 180, the diastolic 110. The retina showed slight perivascular changes only. The urine contained a large amount of albumin, many casts and red blood cells, and a moderate number of leukocytes.

The first sample of blood was withdrawn, without stasis, from the arm vein before breakfast, February 13. At this time there was quite obvious edema of the legs and face. The urine was essentially negative.

March 10, he was admitted to the hospital and given a salt poor diet containing 50 gm. of protein and 2,000 calories, with fluids limited to 1,500 c.c. Diuresis began almost at once and was proceeding rapidly at the time the second blood examination was made, before breakfast on the morning of March 12. However, albuminuria was still profuse. The systolic blood pressure on admission was 168, the diastolic 110; March 13, the systolic was 144, the diastolic 96. The basal metabolism, March 12, was 4.5 per cent. below normal.

The third examination of the blood was made before breakfast, March 22. By this time profuse diuresis had ceased, but he was still losing weight gradually. The systolic blood pressure was 122, the diastolic 84.

The fourth study was made before breakfast, April 5, the day he was discharged from the hospital. The edema had entirely disappeared. The phenolsulphonephthalein excretion was 38 per cent. in two hours and ten minutes. The urine volume was adequate, and he was maintaining his weight at a constant level while receiving 2,500 c.c. of fluids. The basal metabolism, April 3, was — 16 per cent.

He returned before breakfast, April 12, for another blood examination. His general condition was much improved. He had evidently gained considerable weight, but showed no signs of edema. He complained only of slight palpitation on exertion and the fact that he had to get up once or twice each night to urinate. His systolic blood pressure was 118, the diastolic 70. The urine contained only a trace of albumin, moderate numbers of casts and red blood cells. The results of metabolism studies appear in Table 6.

Unfortunately in this case also urine collections were incomplete during the early part of the hospital residence. For the last fourteen days, however, total nitrogen intake and output data are available. The diet was kept constant and contained 50 gm. of protein and 2,000 calories a day. Diuresis continued in a moderate degree for the first days of this period.

The total nitrogen intake was 112 gm., equivalent to 50 gm. of protein a day or 0.79 gm. per kilogram a day. This becomes $112 - 11.2 = 100.8$ after correction for stools. The output was 119.4 gm., leaving a negative balance of $100.8 - 119.4$ gm., representing $\frac{18.6 \times 6.25}{14} = 8.3$ gm. of protein per day. The urinary nonprotein nitrogen was not separately determined, so that neither the quantity of albumin lost nor the absolute protein catabolism can be estimated. The total nitrogen should be corrected for an increase of blood nonprotein nitrogen from 49 to 58 mg. per cent. and a change of weight from 66 to 63.4 kg.

This amounts to $(63.4 \times 0.7)\ (0.49 - 0.58) + (66 - 63.4)\ (0.9 \times 0.49) = 2.9$ mg. This increases the actual nitrogen loss from 119.4 to 122.3 gm., and an actual negative balance of 21.5 gm. equivalent to $\frac{21.5 \times 6.25}{14} = 9.6$ gm. of protein a day.

In this case the administration of 0.79 gm. of protein per kilogram per day with 31 calories per kilogram failed to meet the metabolic requirements of the patient. Whether the negative balance was entirely due to albuminuria or was referable to a high protein catabolism cannot be determined from the data. Qualitative tests of the urine for albumin showed that the latter had decreased considerably during the period of study. That the general metabolism was not unduly elevated is evident from the fact that his basal metabolism on March 12 was 4.5 per cent. below normal and during the latter part of the period of study had fallen to 16 per cent. below normal.

TABLE 6.—*Data in Case 4*

		Fluids				Total Nitrogen			Blood Nonprotein Nitrogen,	Plasma Proteins,
Date	Calories	Intake, C.c.	Urine, C.c.	Balance, C.c.	Weight, Kg.	Intake, Gm.	Urine, Gm.	Balance, Gm.	Mg. per 100 C.c.	per Cent.
March 22.....	2,000	1,300	1,020	280	....	8.0	7.7	0.3	49	6.06
23.....	2,000	1,400	1,000	400	....	8.0	8.0	0.0	..	....
24.....	2,000	1,500	1,460	40	65.5	8.0	11.4	—3.4	..	....
25.....	2,000	1,700	1,380	320	....	8.0	8.4	—0.4	..	....
26.....	2,000	1,800	1,700	100	....	8.0	8.2	—0.2	..	....
27.....	2,000	1,800	1,660	140	....	8.0	7.2	0.8	..	....
28.....	2,000	1,850	1,030	820	....	8.0	5.9	2.1	..	....
29.....	2,000	1,600	1,130	470	....	8.0	6.5	1.5	..	..
30.....	2,000	1,600	1,980	—380	....	8.0	12.3	—4.3	..	....
31.....	2,000	1,650	1,730	—80	64.2	8.0	7.9	0.1	..	....
April 1.....	2,000	2,500	2,160	340	....	8.0	7.3	0.7	..	....
2.....	2,000	2,400	2,600	—200	....	8.0	9.3	—1.3	..	....
3.....	2,000	2,300	1,620	680	....	8.0	7.1	0.9	..	....
4.....	2,000	2,200	1,670	530	63.4	8.0	7.4	0.6	58	5.88
Total.....	28,000	25,600	22,140	3 460	....	112.0	119.4	—7.4		
Daily aver...	2,000	1,829	1,581	248	....	8.0	8.5	—0.5		

CASE 5.—A Greek man, aged 20, was admitted to the hospital, July 3, 1923, complaining of swelling of the legs. About six weeks earlier he began to develop anorexia, general weakness and some epigastric discomfort. Two weeks before he entered the hospital his arms, hands, face and abdomen began to swell without any pain. For a day or two before admission he vomited several times, had slight epistaxis once and noticed some pain in his toes. The past and family histories were entirely unimportant.

At the time of admission the temperature was 97 degrees F., the pulse 78 and the respirations normal in rate and character. The face, arms and trunk appeared puffy and there was distinct pitting edema of the ankles and legs and over the sacrum. The skin and the mucous membranes were pale. The submaxillary lymph nodes were slightly enlarged. The lungs were clear. The heart seemed slightly enlarged to the left; a systolic murmur was heard over the apex and the midcardiac area. The systolic blood pressure was 160, the diastolic 90. The abdomen presented signs of moderate ascites. The liver and spleen were not palpable. Ophthalmoscopic examination revealed no evidences of albuminuric retinitis.

The urine contained large amounts of albumin, many red blood cells and granular and cellular casts. Urine cultures on four occasions, July 4, 7, 10 and August 9, yielded *Staphylococcus albus* and nonhemolytic streptococci. He

had a moderate anemia: the blood count showed 3,600,000 red blood cells; 65 per cent. hemoglobin, and 8,800 leukocytes, with 68 per cent. polymorphonuclear neutrophils. A blood culture proved sterile; the Wassermann reaction was negative. Roentgen-ray examination of the heart and lungs revealed no significant abnormalities. Phenolsulphonephthalein excretion, July 7, amounted to 55 per cent. in two hours and ten minutes.

He was given a diet containing 50 gm. of protein and 2,500 calories, with fluids limited to 1,500 c.c. a day. July 8, because the edema had not diminished the diet was made salt poor. Under this regimen no improvement was noted. Because he exhibited constantly a negative nitrogen balance the diet was increased July 19 to contain 60 gm. of protein and 2,500 calories a day. During the next two weeks the weight diminished gradually from 70.9 to 67.9 kg. and the nonprotein nitrogen of the blood, which had been 82 mg. per cent. July 5, 92 mg., July 10, and 69, July 17, fell to 41, July 20 The blood pressure also fell gradually. August 3, the systolic pressure was 136, the diastolic 74. About the

TABLE 7.—*Data in Case 5*

Date, July	Food. Calories	Fluids			Weight, Kg.	Total Nitrogen			Urine Nonprotein Nitrogen, Gm.	Protein Lost as Albumin, Gm.	Urine Chlorid as Sodium Chlorid, Gm.	Blood Nonprotein Nitrogen, Mg. per 100 C.c.
		Intake, C.c.	Urine, C.c.	Balance, C.c.		Intake, Gm.	Urine, Gm.	Balance, Gm.				
10	2,500	1,550	1,100	450	69.2	8.0	11.2	—3.2	....	....	1.3	92
11	2,500	1,500	1,520	—20	69.4	8.0	13.3	—5.3	....	....	1.5	..
12	2,500	1,650	960	690	69.2	8.0	10.7	—2.7	....	....	0.9	..
13	2,500	1,950	1,240	710	69.1	8.0	12.5	—4.5	....	....	1.4	..
14	2,500	1,800	1,280	520	69.1	8.0	12.7	—4.7	....	....	1.4	..
15	2,500	1,900	1,170	730	....	8.0	11.3	—3.3	....	....	1.5	..
16	2,500	1,900	1,380	520	....	8.0	11.9	—3.9	....	....	1.8	69
17	2,500	2,000	1,080	920	70.9	8.0	10.4	—2.4	7.3	19.8	1.4	..
18	2,500	1,800	1,520	280	70.3	8.0	13.7	—5.7	10.1	22.4	1.3	..
Total	22,500	15,250	11,250	4,800		72.0	107.7	—35.7			12.6	
Daily aver.	2,500	1,694	1,250	533		8.0	12.0	—4.0	....	....	1.4	
August												
17	2,500	1,900	1,850	50	68.7	9.6	7.4	2.2	4.7	16.9	2.4	38*
18	2,500	1,400	1,800	—400	64.0	9.6	9.5	0.1	6.9	21.7	2.9	..
19	2,500	1,800	2,200	—400	62.9	9.6	7.3	2.3	5.4	11.8	3.3	..
20	2,500	2,200	1,830	370	62.9	9.6	9.6	0.0	6.3	20.5	3.6	..
21	2,500	2,000	2,000	0	62.4	9.6	8.4	1.2	6.1	14.5	5.2	..
22	2,500	2,200	2,500	—300	62.4	9.6	10.6	—1.1	7.0	20.0	5.7	..
23	2,500	2,200	2,200	0	62.4	9.6	9.4	0.2	5.9	21.3	4.9	..
24	2,500	2,000	2,500	—300	60.6	9.6	9.2	0.4	6.0	19.6	6.1	..
25	2,500	2,200	3,200	—1,000	60.9	9.6	9.8	—0.2	6.7	19.8	7.4	..
26	2,500	2,000	2,170	—170	59.8	9.6	7.8	1.8	5.1	17.0	5.9	31
Total	25,000	19,900	22,250	—2,150		96.0	89.0	6.8	60.3	183.2	47.3	
Daily aver.	2,500	1,990	2,225	—215		9.6	8.9	0.7	6.0	18.3	4.7	

* Nonprotein nitrogen of August 12.

middle of August the diuresis, which had been progressively diminishing, suddenly increased, and in the last two weeks in the hospital his weight fell from 66.4 to 59.8 kg. The treatment meanwhile had not been changed. At the end of this period the edema had diminished; blood nonprotein nitrogen was only 31 mg. per cent., and he felt so well that he refused to remain in the hospital longer. The albuminuria was quite as profuse as it had been at any time and the urine still contained many red blood cells, leukocytes and casts. There were still slight ascites and vestiges of subcutaneous edema. The anemia had not improved. The daily temperature varied considerably during the first part of his course, frequently rising just above the normal level. The daily swings and the frequency of these abnormal elevations diminished somewhat during the latter part of his stay in the hospital.

Metabolism studies in this case are presented in Table 7. They cover only two periods. During the first, nine days, July 10 to 18, inclusive, he received 50 gm. of protein and 2,500 calories daily, with minimum salt and fluids varying from 1,500 to 2,000 c.c. During the second period of ten days, August 17 to 26, inclusive, he was given a salt poor diet containing 60 gm. of protein and 2,500 calories, and about 2,000 c.c. of fluid a day.

In the first period the nitrogen in the diet amounted to 72 gm., or 8 gm. a days, the equivalent of $\frac{8 \times 6.25}{59.8} = 0.84$ gm. per kilogram a day, on the basis of his weight at the time he was discharged from the hospital. Corrected for loss in stools the available dietary nitrogen comes to $72 \times 0.9 = 64.8$ gm. During the same period he excreted 107.7 gm., leaving a negative balance of -42.9 gm., representing $\frac{42.9 \times 6.25}{9} = 29.8$ gm. of protein a day. The protein lost as albuminuria was only determined for the last two days of the period, when it averaged 21 gm. a day. The blood nonprotein nitrogen was 92 mg. per cent., July 10, and 69, July 16, two days before the study was terminated. The weight increased from 69.2 to 70.3 kg. The nitrogen excretion due to loss of weight and change of blood nonprotein nitrogen came to $(59.8 \times 0.7)\ (0.92 - 0.69) + 0.9\ [0.92\ (69.2 - 59.8) - 0.69\ (70.3 - 59.8)] = 12.4$ gm. The actual nitrogen loss referable to protein catabolism and albuminuria was, therefore, $107.7 - 12.4$ gm., or 95.3 gm. The corrected nitrogen balance, then, becomes $64.8 - 95.3 = -30.5$ gm., or $\frac{30.5 \times 6.25}{9} = 21.2$ gm. of protein a day. This is almost exactly equivalent to the protein lost as albumin on the last two days of the period.

It is evident then, that the administration of 0.84 gm. of protein and 42 calories per kilogram was sufficient to cover the requirements of the nitrogen catabolism but did not suffice to replace the nitrogen lost as albumin in the urine.

During the second period the food nitrogen came to 96 gm., or $\frac{96 \times 6.25}{10 \times 59.8} = 1$ gm. of protein per kilogram a day. Corrected for loss in stools, this becomes $96 \times 0.9 = 86.4$ gm. The urinary nitrogen was 89.0 gm., leaving a negative balance of -2.6 gm., or $\frac{2.6 \times 6.25}{10} = 1.6$ gm. of protein a day. The protein lost as albumin in the urine was 183.2 gm., or 18.3 gm. a day. The urinary nonprotein nitrogen excretion amounted to 60.3 gm. The weight fell from 64.7 to 59.8 kg. and the blood nonprotein nitrogen, which had been 38 mg. per cent., August 12, was 31 mg, August 27. The actual protein catabolism, therefore, amounted to $60.3 - (59.8 \times 0.7)\ (0.38 - 0.31) + (64.8 - 59.8)\ (0.9 \times 0.38) = 55.6$ gm., which is equivalent to $\frac{55.6 \times 6.25}{10} = 34.7$ gm. of protein a day, or 0.57 gm. per kilogram a day.

At first sight it would appear that the mere addition of 10 gm. of protein had resulted in sparing almost double that amount. It is, however, far more probable that improvement in the clinical condition of the patient had been associated with a reduction of the rate of nitrogen catabolism and that this had enabled him to attain nitrogen equilibrium in spite of a profuse albuminuria. One gram of protein and 42 calories per kilogram did not, however, prove sufficient to permit him to repair the effects of previous wastage.

CASE 6.—An American man, aged 34, a mechanic, was admitted to the hospital, Oct. 5, 1923, because pus and blood had been discovered in the urine.

About a month before admission he had had a sore throat. A week later a peritonsillar abscess was drained. Although the pain and edema of the throat and neck subsided rapidly, he did not recover his strength and suffered from indigestion, vomiting frequently after meals. Two days after the abscess was opened he noticed that urination was painful, that he had to void more often than usual, and that his urine was bloody. All these symptoms persisted until he entered the hospital. The past and family histories were entirely negative.

At the time of admission he appeared well developed and nourished and quite comfortable. His color was good; there were no evidences of edema, and temperature, pulse and respirations were normal. The tonsils were enlarged and red; the scar of the operation was still visible, and the pharynx was congested. The systolic blood pressure was 180, the diastolic 90. Physical examination revealed no other abnormalities.

Ophthalmoscopic examination was negative. October 6, the second day in the hospital, numerous fresh conjunctival hemorrhages appeared. The urine was distinctly smoky, and contained a moderate amount of albumin, many red blood cells and leukocytes and a few granular casts. Culture of the urine recovered nonhemolytic streptococci. The blood Wassermann reaction was negative. Phenolsulphonephthalein excretion, October 6, was 65 per cent. in two hours and ten minutes. The blood nonprotein nitrogen was 49 mg. per cent.

TABLE 8.—*Data in Case 6*

		Fluids				Total Nitrogen			Urine Nonprotein Nitrogen, Gm.	Protein Lost as Albumin, Gm.	Blood Nonprotein Nitrogen, Mg. per 100 C.c.	Plasma Proteins, per Cent.
Date, Oct.	Food, Calories	Intake, C.c.	Urine, C.c.	Balance, C.c.	Weight, Kg.	Intake, Gm.	Urine, Gm.	Balance, Gm.				
7	2,500	3,200	1,220	980	71.0	8.0	7.5	0.5	6.5	5.8	49	7.55
8	2,500	2,800	1,980	820	....	8.0	11.0	—3.0	9.2	10.8	..	....
9	2,500	3,800	1,480	2,320	....	8.0	9.1	—1.1	8.1	6.0	..	....
10	2,500	3,000	1,940	2,060	....	8.0	10.5	—2.5	10.1	2.6	..	....
11	2,500	3,600	2,400	1,200	....	8.0	10.5	—2.5	10.0	2.8	..	....
12	2,500	4,000	2,030	1,970	....	8.0	7.9	0.1	7.2	3.9	..	....
13	2,500	3,800	2,200	1,600	....	8.0	8.9	—0.9	8.5	2.8	..	....
14	2,500	3,200	1,920	1,280	....	8.0	7.4	0.6	7.1	2.1	..	....
15	2,500	4,000	3,020	980	69.2	8.0	9.0	—1.0	8.3	4.4	37	....
Total	22,500	31,400	18,190	13,210		72.0	81.7	—11.0	75.1	41.2		
Daily aver.	2,500	3,489	2,021	1,468		8.0	9.1	—1.2	8.4	4.6		

He was given a diet containing 50 gm. of protein, 2,500 calories and large amounts of fluid. With this treatment the urinary changes diminished, the blood nonprotein nitrogen and the blood pressure both fell, and his subjective symptoms rapidly improved. At the end of ten days the urine contained little albumin, moderate numbers of red blood cells and a few leukocytes. Because he had exhibited a negative nitrogen balance the dietary protein was increased to 60 gm., October 16. Improvement continued.

October 26, adenoidectomy and tonsillectomy were performed. There was an immediate but temporary aggravation of the urinary picture followed by an uneventful recovery. At the time of his discharge from the hospital, November 9, the urine contained only a trace of albumin and an occasional red blood cell. The systolic blood pressure was 110, the diastolic 70. The phenolsulphonephthalein excretion was 80 per cent. in two hours and 10 minutes.

Except during the first day in the hospital and the forty-eight hours immediately after operation, the temperature remained normal throughout his stay. At the time of admission he had a moderate anemia, 3,900,000 red blood cells, with 65 per cent. hemoglobin. This condition was improving when he left, the red cells having risen to 4,500,000 and the hemoglobin to 75 per cent. Metabolism studies appear in Table 8.

Metabolism studies in this case were quite incomplete because urine collections were unsatisfactory. It is, however, possible to draw some conclusions from the first period of nine days, October 7 to 15, inclusive. During this period he received 72 gm. of nitrogen in the diet or, correcting for loss in stools, 65 gm. of available nitrogen, and excreted in the urine 82 gm., leaving a negative balance of 17 gm., representing $\frac{17 \times 6.25}{9} = 11.8$ gm. of protein a day. During the same period he lost as albumin in the urine 41 gm. of protein, or 4.6 gm. a day. The administration, therefore, of 0.71 gm. of protein and 36 calories per kilogram a day did not suffice to prevent nitrogen wastage. The urinary nonprotein nitrogen was 75 gm. This must be corrected for a loss of weight from 71 to 69.2 kg. and reduction of the blood nonprotein nitrogen from 49 mg. per cent. to 37. In this case there was no edema and the loss of weight is presumably referable to actual tissue wastage. The nitrogen catabolism, therefore, amounts to $75 - (71 \times 0.7 \times 0.49) - (69.2 \times 0.7 \times 0.37) = 69$ gm. This represents $\frac{69 \times 6.25}{9} = 47.9$ gm. of protein per day, or 0.68 gm. per kilogram a day. In view of the probability that urine collections were incomplete, this must be considered as a minimal value.

In this case, during the acute stage of the disease, the administration of 0.71 gm. of protein and 36 calories per kilogram a day was not enough to prevent nitrogen wastage. The loss in this instance cannot be ascribed entirely to the albuminuria, which was relatively slight. The subsequent course does not permit an evaluation of the effect of altering the diet. Apparently, he attained equilibrium and a positive nitrogen balance as soon as the diet was increased. Even if it is assumed that the urine collections were complete, the clinical condition and albuminuria improved so considerably at the same time that the metabolic alteration cannot be attributed to the dietetic changes alone.

COMMENT

From these studies certain general conclusions can be drawn. In the first place it is quite evident that by the proper regulation of diet it is possible to replace nitrogen lost as albumin. This cannot, however, be effected unless allowance is specifically made for such loss. The use of comparatively high caloric diets with a considerable excess of fat and carbohydrate in this, as in other conditions, results in the reduction of the nitrogen metabolism. By means of such high caloric diets the protein catabolism, as measured by the nonprotein nitrogen output, reaches levels quite as low as, but no lower than, those reported in other conditions, from 0.5 to 0.7 gm. per kilogram a day. Over and above this minimum a sufficient excess of protein must be given to replace albuminuric nitrogen.

Most of these patients, when they are given an adequate excess, exhibit a tendency to store large amounts of protein over considerable periods, in one case for almost three months. This is probably evidence that they have undergone protein starvation during the preceding period. It is quite impossible to say how much of this has been due to mis-

directed dietetic treatment and how much to the fact that the disease itself is associated with an augmented nitrogen metabolism. Some of the patients had received little or no dietary treatment before they came to the hospital so that restriction of diet probably played only a minor part in the production of the protein wastage. The wasting character of the disease has been too little stressed in earlier studies. Emaciation was evident in this series in every instance when the disease had lasted more than a short time. It became obvious, however, only after the edema had disappeared. The latter lends to most of the patients a specious appearance of being well nourished.

The administration of protein in excess of that required to meet the needs of nitrogen catabolism and replacement of the protein lost as albumin in the urine results in the storage of nitrogen. This presumably goes to the restoration of depleted tissue protein. Increasing the protein in one case to 75 gm. from 60 gm. resulted in the storage of almost the entire additional protein. How far this process could be continued to advantage it is impossible to tell. It is highly improbable that a true high protein diet limited in fat or carbohydrate or both would be relatively as effective. Adequate fat and carbohydrate are essential factors in the production of low nitrogen catabolism. A large part of the success obtained has been due to the fact that the nitrogen catabolism was reduced to a low level, thus releasing as much protein as possible for other purposes.

The general practice of using total nitrogen excretion as a measure of nitrogen metabolism cannot be applied to nephritic studies. Nitrogen lost as albumin in the urine has obviously played no useful part in the metabolic processes of the body. If this is not taken into consideration the nitrogen metabolism is likely to be exaggerated. In estimating the true protein catabolism, changes in the weight of the subject and in the level of the blood and tissue nonprotein nitrogen must also be taken into consideration. A positive nitrogen balance cannot be interpreted as evidence of inability on the part of the kidney to excrete protein waste products; nor is a negative balance a sign that the individual is overcoming the effects of such a retention. This has already been brought out by Mosenthal and Richards [3] and others. The nitrogen balance and the level of the blood nonprotein nitrogen are only indirectly dependent on the amount of protein in the diet and are only partly determined by the functional state of the kidney. The rate of nitrogenous metabolism in these cases appears to be the chief determinant of the level of blood nonprotein nitrogen. The latter has been elevated only in periods when the metabolism was relatively high and usually when there was a negative nitrogen balance. Increasing dietary protein can then be expected to raise the nonprotein nitrogen of the blood only if it raises the protein

metabolism of the body. When such an increase contributes only to the restoration of depleted tissue, it has no such effect.

In all but one of the cases discussed above the blood nonprotein nitrogen was elevated during the early part of the course, falling to the normal level as the disease improved. Many factors probably contribute to the production of the azotemia. Although the ability of the organism to concentrate metabolites in the urine is relatively unimpaired in most instances, this impairment is rendered more serious by reason of the associated oliguria. In addition to these factors, however, a relatively large nitrogen catabolism usually plays an important rôle. When the latter has ceased the azotemia has disappeared even when the urine volume remained scanty. It is important to ascertain the underlying cause of this high protein metabolism as a guide to the treatment of the more acute stages of nephritis. It is easy to ascribe the observed reductions of metabolism to effective dietetic therapy. They may quite as well have been due to variations in the course of the disease itself. Whether the high nitrogen catabolism of the acute stages can be controlled is as yet undetermined. It is reasonably certain that it can be favorably influenced by measures similar to those which have been employed in these cases. The few patients in our series who have progressed unfavorably have presented complicating conditions that have made metabolism studies impossible or unintelligible.

That the stage of the disease may be the predominant factor in determining the nonprotein nitrogen is suggested by some studies on the effect of urea administration in Case 2. After improvement had set in urea was given to this patient in an attempt to hasten diuresis. In this respect it was comparatively ineffectual but it did not provoke an azotemia. Although the amounts of urea administered were smaller than those advocated by McLean, they were sufficient to raise the nonprotein nitrogen output well above the level at which, at an earlier stage, he had shown definite azotemia. From this one cannot argue that his ability to excrete nitrogen was normal; there was a certain delay in the excretion of the urea that has not been observed in normal persons. His powers of compensation were, however, not overtaxed and he was quite able to take care of the load of added urea without significant alteration of the blood nitrogen.

In all the cases here presented, with a possible single exception, the disease had an infectious origin, or at least began immediately after a definite infection. The urines, at least in the acute stages, contained red blood cells and leukocytes in varying numbers as well as albumin and casts. During the same stages blood pressure and nonprotein nitrogen were also somewhat elevated. With the one exception noted above, Case 3, none of them could have been admitted into the group which

Müller,[10] Epstein,[4] and Volhard and Fahr [1] have called nephrosis. At the same time they present many of the phenomena characteristic of this condition: the tendency to edema, profuse albuminuria, and especially reduction of plasma proteins. Case 3 gives the typical history and clinical signs of nephrosis. The disease in his case developed insidiously and, while he was under observation, blood pressure and nonprotein nitrogen were never elevated and hematuria was not observed.

At first sight there seems to be a real difference between the two types of cases. On closer analysis, however, the distinction becomes less convincing. In all the "infectious" cases, as the acute stage of the disease subsides hematuria, hypertension and azotemia diminish. Sometimes this leads to the production of a condition, as for example in the latter stages of the hospital course of Case 2, that is entirely indistinguishable from that of nephrosis. Granted that the two are separate entities, clinical differentiation is exceedingly difficult if hematuria, hypertension and azotemia are the only distinguishing features, because the latter are not persistent in cases that have an admitted nephritis. It is not inconceivable that "nephrosis" is only a more or less quiescent stage of a nephritic process and that the "insidious onset," which is so much emphasized, masked the symptoms of an acute stage. It has been long recognized and is apparent from these studies that nephritis seldom develops during the acute stages of the infection that causes it, but usually begins during convalescence from the primary disease. For this reason connection with the etiologic factor is often overlooked. Certainly differential diagnosis of the two conditions is impossible from a clinical standpoint except after prolonged observation.

Epstein [11] asserts that the basal metabolism of true nephrosis cases is regularly low. Both he and Eppinger [12] advocate thyroid treatment for this reason. A few basal metabolism determinations were made in this series but showed no consistent changes; they varied from + 16 to — 16 per cent. In the one typical nephrosis case values of + 16 and — 5 per cent. were obtained. These alterations are of doubtful significance. It is possible that Epstein's low figures and our own are merely another expression of the undernutrition exhibited in the nitrogen metabolism. Two cases (Cases 3 and 4) had more than one determination. In both instances the second, made when the condition of the

10. Müller, Friedrich: Bezeichnung und Begriffsbestimmung auf dem Gebiete der Nierenkrankheiten, 1917.

11. Epstein, A. A.: Further Observations on the Nature and Treatment of Chronic Nephrosis, Am. J. M. Sc. **163**:167 (Feb.) 1922.

12. Eppinger, Hans: Zur Pathologie und Therapie des menschlichen Odems zugleich ein Beitrag zur Lehre von der Schilddrusenfunktion, Eine klinisch experimentelle Studie, Berlin, 1917.

patient was improved, was the lower, conforming to the nitrogen metabolism changes.

In two cases tonsillectomy was performed in order to remove the infection that had provoked the nephritis. In both instances favorable end-results were obtained, although in one there was an immediate exacerbation of the nephritis. In another case tonsillectomy proved entirely ineffectual. It is important to note that in this last case the operation had quite as little effect in preventing respiratory infections. Throughout his stay in the hospital Patient 1 had recurrent exacerbations of hematuria, attended in each case with mild sore throat, coryza and temperature. Concerning the mechanism that connects the infections with the nephritis only speculation is possible. One gains the impression from this case and others that there is some connection between the two in certain cases and that anything that tends to prevent infections will also check the progress of the renal disease. When tonsillectomy has such an effect it may be a beneficial procedure. The indiscriminate removal of suspected organs is not, however, advisable nor likely to have any favorable effect.

In every case except one (Case 1) in which the urine was cultured, organisms were recovered, usually nonhemolytic streptococci. This cannot be accepted as definite evidence that these cocci were the cause of the infection because of the notorious difficulty of obtaining urine free from contaminating bacteria. The probability that the organisms actually came from the deeper portions of the urinary tract is somewhat increased in those cases in which they were obtained on several occasions. In all instances the urine was collected in a series of tubes and only those cultures are reported as positive in which the same organism was recovered from all tubes, usually in both smear and culture. If these bacteria are to be accepted as the etiologic agents of the nephritis one must postulate some kind of a diffuse, sluggish infectious process of hematogenous origin in which the organisms are established in the renal tissue, a condition that pathologists rarely encounter. In this case it is hard to see how removal of the original focus of infection in the tonsils can benefit the condition.

The fact that nephritis seldom develops until the primary infectious process is subsiding also argues against a direct infection of the kidney unless it is presumed that the renal lesion begins during the more acute stages of the infection but requires a certain period to develop to the point of producing symptoms. How further exacerbations or recurrences of the original remote focus may affect the kidney lesion is also obscure. Until some of these questions are answered, however, treatment directed toward the cure of the disease can have no rational basis.

Discussion of the changes in plasma proteins, electrolytes, diuresis and water balance will be reserved for subsequent articles.

SUMMARY AND CONCLUSIONS

A study of the nitrogen metabolism of certain patients with acute and chronic parenchymatous nephritis has been made in an attempt to determine to what extent protein lost as albumin in the urine can be replaced by food protein.

1. The total urinary nitrogen of these patients is not a satisfactory measure of nitrogen catabolism.

2. The nitrogen catabolism can only be estimated from the urinary nonprotein nitrogen after proper allowance has been made for changes in blood and tissue nonprotein nitrogen and variations of body weight due to diuresis or accumulation of edema.

3. By the administration of large amounts of carbohydrate and fat it has proved possible to reduce the protein catabolism to from 0.5 to 0.7 gm. per kilogram a day.

4. If enough protein is given to cover the nitrogen catabolism plus an additional amount equivalent to that lost as albumin in the urine, nitrogen wastage may be prevented.

5. Most of these patients when they enter the hospital show evidences of previous protein deficiency. If they are given more than enough protein to replace the amount lost in the urine, they will store the excess within certain limits, thus repairing the effects of previous nitrogen wastage.

6. This protein wastage may be partly due to early dietary mismanagement. The loss of protein as albumin in the urine is certainly a serious contributory cause. It also seems probable that the disease itself, in its more acute stages at least, is characterized by a higher protein metabolism than normal. This is suggested by the results of these studies.

7. Abnormally high blood nonprotein nitrogen has only been observed when the nitrogen catabolism was relatively high and has usually returned to the normal level as the clinical condition of the patient improved and the nitrogen catabolism diminished.

METHODS AND RESULTS OF OXYGEN TREATMENT IN PNEUMONIA *

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The object of this investigation is to secure further information concerning the importance of oxygen as a therapeutic agent. In the first part of the paper, evidence will be presented bearing on the effectiveness of certain methods of administering oxygen; in the second part, a report will be made of the results of oxygen treatment by the more desirable of these methods.

Pharmacologic experience demonstrates that the therapeutic activity of a drug is closely related to the dosage employed. Such a conception, however, has had very little application to the therapeutic use of oxygen. Inefficient methods of administration and the absence of any precise knowledge as to how much oxygen the patient actually receives appear to be important factors accounting for the confusion surrounding the subject. It seems of value to define the limitations of a few commonly used methods and to inquire into the qualifications of an effective method, for it is obvious that any final judgment of the importance of oxygen as a therapeutic agent must be postponed until the factor of dosage is adequately considered.

In recent years the introduction of adequate methods, the recognition of oxygen deficiency in the arterial blood in patients with pneumonia and several controlled reports of effective treatment have led to a decidedly more favorable opinion than was previously held. However, the compiled results of controlled oxygen treatment in pneumonia are based on fewer than fifty cases.[1] In this article the clinical and laboratory data of sixteen additional cases will be discussed. The theoretical basis of oxygen therapy and the indications for its use have been considered elsewhere.[2]

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1. Meakins, J. C.: The Therapeutic Value of Oxygen in Pulmonary Lesions, Brit. M. J. **1**:324 (March 6) 1920; Observations on the Gases in Human Arterial Blood in Certain Pathological Conditions and Their Treatment with Oxygen, J. Path. & Bacteriol. **24**:79 (Jan.) 1921. Means, J. H., and Barach, A. L.: The Symptomatic Treatment of Pneumonia, J. A. M. A. **77**:1217 (Oct. 15) 1921. Barach, A. L., and Woodwell, M. N.: Studies in Oxygen Therapy, II, In Pneumonia and Its Complications, Arch. Int. Med. **28**:394 (Oct.) 1921. Stadie, W. C.: The Treatment of Anoxemia in Pneumonia in Oxygen Chamber, J. Exper. Med. **35**:337 (March) 1922. Hastings, A. B.; Neill, J. M.; Morgan, H. J., and Binger, C. A. L.: Blood Reaction and Blood Gases in Pneumonia, J. Clin. Invest. **1**:25, 1924.

2. Barach, A. L.: The Therapeutic Use of Oxygen, J. A. M. A. **79**:693 (Aug. 26) 1922. Means, J. H.: Dyspnea, Medicine **3**:309 (Aug.) 1924.

The effective administration of oxygen apparently began in the year 1917 when the Haldane apparatus was used in the treatment of acute pulmonary edema of war gas poisoning.[3] During the same year Meltzer [4] reported the successful use of the oral insufflation apparatus. In 1921 Barach and Woodwell [5] described a rebreathing apparatus for cases of pneumonia and cardiac insufficiency. Henderson [6] in 1922 described an apparatus employed in resuscitation from gas poisoning and suggested its use in pneumonia. Since 1921 oxygen chambers have been used by Barcroft [7] and Poulton [8] in England and by Stadie [9] and Binger [10] in this country. A bed tent was described by Hill,[11] a head tent by Roth [12] and recently a portable oxygen tent by Barach and Binger.[13] The nasal catheter was introduced during the war and has been widely used since then. The oldest and still the most common method is the administration of oxygen by a funnel held in front of the patient's face. The administration of oxygen intravenously, subcutaneouly or by rectum will not be considered as these methods seem to have little theoretic basis. Ordinarily, the inspired air contains approximately 21 per cent. oxygen. The methods that have been used vary so widely that the inspired air may contain anywhere from 21 to 100 per cent. oxygen. It is probable that oxygen to be of therapeutic potency should be administered at a certain optimal concentration and within a certain maximal and minimal range.

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3. Haldane, J. S.: Therapeutic Administration of Oxygen, Brit. M. J. **1**:181 (Feb. 10) 1917.

4. Meltzer, S. J.: Therapeutic Value of Oral Rhythmic Insufflation of Oxygen, J. A. M. A. **69**:1150 (Oct. 6) 1917.

5. Barach, A. L., and Woodwell, M. N.: Studies in Oxygen Therapy, I, In Cardiac Insufficiency and Related Conditions, Arch. Int. Med. **28**:367 (Oct.) 1921. Barach, A. L.: A Simple Apparatus for Administering Oxygen, J. A. M. A. **78**:334 (Feb. 4) 1922.

6. Henderson, Yandell; and Haggard, H. W.: Report 1 of Commission of Resuscitation from Carbon Monoxid Asphyxia to American Gas Association, J. A. M. A. **79**:1137 (Sept. 30) 1922.

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8. Campbell, J. M. H.; Hunt, G. H., and Poulton, E. P.: An Examination of the Blood Gases and Respiration in Disease, J. Path. & Bacteriol. **26**:234 (April) 1923.

9. Stadie (Footnote 1, fourth reference).

10. Binger, C. A. L.: The Construction and Management of an Oxygen Chamber, Mod. Hosp. **24**:186 (Feb.) 1925.

11. Hill, Leonard: A Simple Oxygen Bed Tent and Its Use in a Case of Edema and Chronic Ulcer of the Leg, J. Physiol. **50**, May 24, 1921; Proc. Physiol. Soc., p. 20.

12. Roth, Paul: Improved Apparatus for the Therapeutic Administration of Oxygen, Mod. Hosp. **22**:404 (April) 1924.

13. Barach, A. L., and Binger, C. A. L.: A Portable Oxygen Tent, J. A. M. A. **85**:190 (July 18) 1925.

We have come to the conclusion that the inspired air should contain between 30 and 60 per cent. oxygen before oxygen administration can be definitely considered a therapeutic agent, and that for most cases 40 per cent. seems optimal. The maximum concentration at which oxygen may be administered with safety is 70 per cent. When animals are exposed to air mixtures containing more than 70 per cent. oxygen for from one to four days death may ensue as a result of an acute serous pneumonia.[14] Air mixtures of 70 per cent. oxygen are said to be without danger for this period of time. We have kept animals in an oxygen chamber containing 60 per cent. oxygen for periods as long as six months without harmful effects.[15] It seems advisable therefore to administer oxygen continuously in concentrations not exceeding 60 per cent. In our experience the majority of pneumonia patients with oxygen deficiency recorded in their arterial blood are restored to or near the normal value by breathing air containing 40 per cent. oxygen. Although clinical and laboratory data indicate that 30 per cent. oxygen may register some improvement in the mild and occasionally in the severe cases of arterial anoxemia, the majority of cases are not much improved until from 40 to 50 per cent. of oxygen is administered. A method, then, that is capable of providing 40 per cent. or more oxygen may be ranked as effective, one that provides 30 per cent. oxygen as slightly effective, and one that provides less than 30 per cent. as relatively ineffective.

The cause of arterial anoxemia in pneumonia depends on the type of lung involvement. If a blood flow is present through consolidated lung, as may happen in the early stage of the disease, even the highest concentration of oxygen will be unable to make up for the deficiency created by unventilated blood entering the aortic stream, a circumstance that is explained by the oxygen absorption curve of hemoglobin. Edema and congestion of alveolar walls appear to be more common factors, with possible additional influences, such as shallow breathing and altered pulmonary diffusion. Under these conditions increased concentrations of oxygen penetrate the alveolar wall and overcome the arterial anoxemia. The theoretical aspects of this subject have recently been clearly presented by Lundsgaard and Van Slyke.[16]

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14. Smith, J. L.: The Pathological Effects Due to Increase of Oxygen Tension in the Air Breathed, J. Physiol. **24**:19, 1899. Karsner, H. T.: The Pathological Effects of Atmosphere Rich in Oxygen, J. Exper. Med. **23**:149 (Feb.) 1916.

15. Barach, A. L.: The Effect of the Inhalation of Oxygen over Long Periods of Time on Normal Rabbits and Rabbits with Pulmonary Tuberculosis, to be published.

16. Lundsgaard, Christian; and Van Slyke, D. D.: Cyanosis, Medicine **2**:1 (Feb.) 1923.

METHODS

The two methods first investigated were the tube and funnel and the nasal catheter. In each case samplings of air were taken from the nasopharynx during the administration of oxygen. A small tube or catheter was passed into the nasopharynx, and the projecting end directly connected with the simplified oxygen analyzer described by Binger.[10] In this method the maximum error is 0.5 per cent., an accuracy sufficient for the purpose. A gauge especially calibrated to deliver oxygen in liters per minute was used in conjunction with high pressure oxygen tanks. In sampling the nasopharyngeal air it was not possible to obtain inspired fractions separate from expiratory fractions, so that a mixture was commonly obtained from both phases, both in the patients with pneumonia and in the normal subject tested. This gives a reading of approximately 19.5 per cent. for the nasopharngeal air, instead of 21 per cent. for the air inspired.

1. *Tube and Funnel.*—In this method, oxygen is bubbled through a water bottle, from which it is conducted by a rubber tube to a glass funnel held in front of the patient's nose and mouth. The distance from the face as well as the amount of oxygen bubbled through the bottle varies widely. In the following experiments the funnel was held one-half inch (1.27 cm.) from the nose and oxygen run from the tank at (1) 0.5 liter per minute; (2) 1 liter, equivalent to fairly vigorous bubbling, and (3) 2 liters per minute. The results are seen in Table 1.

TABLE 1.—*Effect of Administration of Oxygen Through Funnel on Oxygen Concentration of Nasopharyngeal Air in Patient with Pneumonia*

Oxygen Flow Through Funnel, Liters per Minute	Respiratory Rate per Minute	Oxygen Concentration of Nasopharynx, per Cent.
None	48	19.0
0.5	48	20.0
1.0	48	20.5
2.0	48	22.0

It is seen that the nasopharyngeal air may be practically unchanged or at the maximum may contain 22 per cent. oxygen, indicating approximately 24 per cent. oxygen in the inspired air. No change in cyanosis or breathing was manifest. These results confirm the clinical impression that the funnel method is practically useless.

2. *Nasal Catheter.*—The nasal catheter is said to have been introduced by Captain Stokes[17] during the war for treatment of the acute pulmonary edema caused by gas poisoning. It was often used in place of the Haldane apparatus, in which a mask was applied to the patient's face. The comments of the men who used both methods are of interest. Douglas[17] found the Haldane apparatus very effective and the nasal

17. Stokes: Discussion on Therapeutic Use of Oxygen, Proc. Roy. Soc. Med. (Sect. Therap. and Pharmacol.) **13**:59, 1920.

catheter less effective. Cummins [17] found it difficult to use the mask because of the discomfort it provoked. Ryle [17] used the nasal catheter with fairly good results. Masks were improvised at his station but were not tolerated by the men. Hamil [17] considered the nasal tube satisfactory but wasteful and also found the mask badly tolerated, especially in warm climates. Hoover [18] said that the gassed men begged to be relieved of the mask and preferred to have the oxygen conducted by a soft rubber tube in their nostrils, though by the latter method he did not see a single case in which the cyanosis was diminished. Similar differences in opinion are found in clinics where the nasal catheter has since been used.

The foregoing differences seem to be due in part to the variable effectiveness of the catheter method. In the first place the catheter may be placed in the anterior nares, or be plugged by nasal secretions, or have only one opening at the end, which may be closed by contact with the nasal mucous membrane. The rate at which oxygen is bubbled through the water bottle is another variable factor. In our observation it was often 0.5 liter per minute and occasionally 1 liter per minute. With the low pressure tanks in universal use oxygen begun at 1 liter per minute in one hour falls to 0.5 liter per minute unless readjusted.

It is possible to calculate the degree of oxygen enrichment that the nasal catheter may furnish from the tidal air, the respiratory rate and the oxygen administered in liters per minute (Table 2 for data on pneumonia patients with different pulmonary ventilation under varying conditions of oxygen flow). For example, if 1,000 c.c. of oxygen per minute is run into the nasopharynx the amount inhaled is the portion that runs in during inspiration, the exhaled air obviously containing the oxygen run in during expiration. If the rate of respiration is 40 per minute, the oxygen added to each inspiration is ½ by 1/40 by 1,000 c.c., or 12.5 c.c. If the tidal volume is 300 c.c., the oxygen content of the inhaled air is 63 + 12.5, or 75.5 c.c., or 25.2 per cent. of the inspired air. Thus, when the nasal catheter is used with oxygen bubbling fairly vigorously, the oxygen concentration of the inspired air is 25.2 per cent. If oxygen is admitted at the rate of 2,000 c.c. per minute, a large amount for a nasal catheter, the oxygen percentage of the inspired air is in this instance 30.6 per cent.[19]

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18. Hoover, C. F.: Oxygen Therapy, J. A. M. A. **71**:880 (Sept. 14) 1918.

19. Inspiration is generally shorter than expiration, the time kept by the two phases being in the proportion 10:12. The pause between two respirations lasts from about one-third to one-fifth of the total time between the beginning of one inspiration and the next (Schafer's Psysiology **11**:281). Vierordt (Anatomische, Physiologische und Physikalische Daten und Tabellen, p. 258) gives the time for the total respiratory excursion as from 3 to 3.8 seconds, and the ratios of inspiration and expiration variously as 8:12, 10:12, 9:13. In respiratory disease expiration may be further lengthened. For purposes of approximate calculation of the amount of oxygen admitted during inspiration we have chosen a 1:1 ratio.

TABLE 2.—*Effect of Administration of Oxygen Through Nasal Catheter on Oxygen Concentration of Inspired Air Calculated for Pneumonia Patients Under Varying Conditions of Oxygen Flow*

Oxygen Flow Through Catheter, Liters per Minute	Respiratory Rate per Minute	Tidal Volume, C.c. per Inspiration	Duration of Inspiration, Minutes	Oxygen Added per Inspiration, C.c.	Oxygen of Inspired Air, per Cent.
None	40	250	0.012	....	21.0
500	40	250	0.012	6.0	23.4
1,000	40	250	0.012	12.0	25.8
2,000	40	250	0.012	24.0	30.6
500	50	250	0.010	5.0	23.0
1,000	50	250	0.010	10.0	25.0
2,000	50	250	0.010	20.0	29.0
500	40	200	0.012	6.0	24.0
1,000	40	200	0.012	12.0	27.0
2,000	40	200	0.012	24.0	33.0

That this method of reasoning is approximately correct may be seen by reference to Table 3, which gives data obtained from a patient with pneumonia. It is seen that the nasopharyngeal air contained 22 per cent. oxygen when 500 c.c. of oxygen was administered, 25 per cent. when 1,000 c.c. of oxygen was administered, and 30 per cent. when 2,000 c.c. of oxygen was the rate of flow through the catheter.

TABLE 3.—*Effect of Administration of Oxygen Through Nasal Catheter on Oxygen Concentration of Nasopharyngeal Air in Patient with Pneumonia*

Oxygen Flow Through Funnel, Liters per Minute	Respiratory Rate per Minute	Oxygen Concentration of Nasopharynx, per Cent.
None	48	19.0
0.5	48	22.0
1.0	48	25.0
2.0	48	30.0

If oxygen is administered to a subject with an intact respiratory apparatus, more oxygen is added per inspiration, but the increased tidal air partially counterbalances this effect, thus keeping the concentration of oxygen in the air breathed at similar low levels. An experiment was performed on a control subject who attempted to breathe approximately the character of pulmonary ventilation found in normal respiration and in pneumonia. The results are seen in Table 4.

The calculated results are slightly higher than those actually obtained, owing to the admixture of expiratory fractions in the latter. They confirm previous calculations and results on pneumonia patients, namely, that the concentration of oxygen in the inspired air may vary between 22 and 35 per cent., depending on the rate of flow. When 1 liter a minute is the amount administered, the concentration of oxygen in the inspired air through the use of the nasal catheter is from 25 to 27 per cent.

One exception to these conclusions must be emphasized. If the oxygen is administered by nasal catheter in a patient who breathes

through his mouth the inspired air may not be enriched but consists mostly of room air. The oxygen passes in and out of the nose, gradually elevating the oxygen concentration of the nasopharynx, whereas the pharynx through which respiration is being accomplished may contain only 21 per cent. oxygen. This may be an added factor accounting for the discrepancy in the results of catheter oxygen treatment.

If oxygen is bubbled at the vigorous rate of 2 liters a minute, the pneumonia patient may receive approximately 30 per cent. oxygen, which places this method in the slightly effective classification. In order to accomplish this degree of effectiveness the following points have been found helpful:

TABLE 4.—*Effects of Administration of Oxygen Through Nasal Catheter on Oxygen Concentration of Inspired Air of Normal Individual: (1) Calculated for Quiet Breathing and for Induced Dyspnea; (2) Actually Obtained in Nasopharynx*

Oxygen Flow Through Catheter, Liters per Minute	Respiratory Rate per Minute	Tidal Volume, C.c. per Inspiration	Duration of Inspiration, Minutes	Oxygen Added per Inspiration, C.c.	Calculated Oxygen of Inspired Air, per Cent.	Obtained Oxygen of Nasopharynx, per Cent.*
None	18	500	0.0278	....	21.0	19.5
0.5	18	500	0.0278	13.9	23.8	22.0
1.0	18	500	0.0278	27.8	26.5	25.0
2.0	18	500	0.0278	55.6	32.1	30.0
0.5	40	250	0.012	6.0	23.4	21.5
1.0	40	250	0.012	12.0	25.8	25.0
2.0	40	250	0.012	24.0	30.6	29.0

* These figures represent mixtures of inspired and expired air, and are, therefore, apt to be lower than the inspired air by from 1 to 2 per cent.

1. A catheter of small diameter, such as a No. 10 F, is to be preferred because the larger sizes are more uncomfortable and more apt to cause mouth breathing.

2. It is advisable to have four holes placed within the terminal 1 inch (2.5 cm.) of the catheter as clogging is less apt to take place, and as the high rate of flow is better tolerated than when one hole is present. In the latter instance a vigorous stream of oxygen directed against the nasopharynx causes a painful burning sensation.

3. The catheter should be cleaned at least every four hours.

4. It should be put in place, preferably by a physician, by passing it along the inferior surface of the nasal cavity until it strikes the posterior surface of the nasopharynx; then it should be withdrawn one-half inch (1.27 cm.), passed over the forehead and fastened there with adhesive.

5. When 2 liters a minute causes an uncomfortable sensation, two catheters should be used with a connecting Y tube. Some patients, however, complain of suffocation with two catheters; others institute mouth breathing, and with them one catheter must be employed.

6. High pressure oxygen tanks seem the best way to employ this kind of therapy with any assurance of a constant rate of flow. The low pressure tanks cannot be regulated at a given flow because the diminishing pressure results in a gradually lessening output. They are not equipped with a gage. Furthermore, the expense of low pressure tanks is almost prohibitive if 2 liters of oxygen per minute is prescribed.

This aspect of the question is of importance both from the standpoint of the hospital and that of private patients, and warrants further consideration.

At 2 liters a minute the oxygen consumed in twenty-four hours is 2,880 liters, or 103 cu. ft. There are in general three common low pressure tanks available, large, medium and small size. In the medium size the charge to the hospital is 8.7 cents a cu. ft., or approximately $9 for one day's treatment to one person, and $63 for one week. For the small size the charge is 13.5 cents a cu. ft., or approximately $14 for one day and $100 for one week. With high pressure oxygen either in the large or small size tanks the charge is 1.55 cents a cu. ft., or $1.60 a day and $11.20 for one week. In outside private practice, the cost of low pressure oxygen tanks may be three or four times as much, whereas high pressure oxygen costs only one-half again as much as the hospital charge. Furthermore, a large low pressure tank would have to be changed four times in twenty-four hours, a medium size tank eight times, a small low pressure tank ten times, and a small high pressure tank only once. A large high pressure tank at the same rate of flow, i. e., 2 liters per minute, lasts more than two days.

The disadvantages of the high pressure oxygen tank are the increased weight and the fact that a reducing valve has to be attached to the tank before it is used. We have employed rubber wheeled trucks for the large and small high pressure tanks; these make them easy to move from ward to ward by nurse or orderly. With all types of high pressure oxygen tanks care in adjustment of the reducing valve is necessary to prevent accidents.

3. *Haldane Method.*—This method has the advantage of an approximate regulation of the concentration of oxygen administered. In our hands the use of a face mask limits its application largely to comatose or apathetic patients because of the feeling of suffocation it engenders. The Henderson apparatus carries a little further the regulation of the oxygen concentration of the air breathed but likewise utilizes a face mask.

4. *Rebreathing Apparatus.*—In this method, rebreathing of oxygen was instituted, soda-lime being used to absorb carbon dioxid. When we first employed the method five years ago a mouthpiece of glass or rubber was inserted between the lips and teeth. The patient breathed oxygen through his mouth and diluted this with air from his nose. It was more comfortable than a mask but many patients objected to its use over long periods. Furthermore, regulation of the oxygen concentration was difficult. Recently, we have substituted glass nose-pieces of varying size which are connected in circuit as the mouthpiece was. It consists of two glass tubes which fit into each nostril at one end and fuse at the other to make a single large glass tube, which is connected by appropriate tubing to the rest of the apparatus. For the average case one of the glass tubes is closed by a small cork and is not

used, and the other fits accurately into one nostril. In this way the patient breathes room air through one nostril and oxygen through the other.

Often a piece of thin rubber tubing about 5 inches (12.7 cm.) in length and of the same diameter as the glass tubing is led off from the nose-piece and inserted into the nostril. This allows more movement on the part of the patient without disturbing the breathing of oxygen.

Theoretically, this affords a final mixture in the nasopharynx of 60 per cent. oxygen, but actual measurements by catheter in situ demonstrate that 40 per cent. is the rule. This is due to the fact that the apparatus when treatment is begun contains room air which tends to be gradually replaced by pure oxygen from the tank, although never completely because the exhaled air contains a varying proportion of nitrogen which dilutes the oxygen coming from the tank. It is more saving of oxygen to use a large nose-piece, with only one tube inserted into a nostril than two tubes of a small nose-piece inserted into both nostrils. This method is more satisfactory both from the standpoint of providing a 40 per cent. oxygen mixture and from the standpoint of comfort of the patient than any portable apparatus we have encountered. In addition 1 liter of oxygen per minute keeps the rebreathing bag full and allows for all the waste. For this reason its efficiency on the basis of cost is proportionately great, when we consider that 1 liter from the nasal catheter provides a 25 per cent. oxygen mixture. When patients breathe wholly through their mouth the mouthpiece has to be resorted to. There are patients, however, who will not submit to any appliance to the face whatever. For them an oxygen rich atmosphere must be provided.

5. *Portable Oxygen Tent.*—Binger and myself have recently constructed a portable oxygen tent that has many of the advantages of an oxygen chamber with the additional benefits of portability and decreased cost. It encloses the entire patient in bed, is equipped with four windows, and is ventilated by a closed circuit power box which accomplishes the removal of carbon dioxid, moisture and heat. The oxygen tent secures comfort for the patient and provides for the precise regulation of the oxygen concentration desired. Most of the results in this paper are derived from the oxygen tent and the rebreathing apparatus.

RESULTS

Sixteen patients ill with pneumonia were treated with oxygen, ten in the portable oxygen tent and six by a combination of rebreathing apparatus and nasal catheter. These patients were selected because of the presence of arterial anoxemia. A summary of the clinical and laboratory data is given in Table 5. The individual case histories follow.

TABLE 5.—*Effect of Oxygen Treatment on Arterial Blood Gases and Clinical Conditions in Sixteen Cases of Pneumonia*

Case	Age	Diagnosis	Date	Oxygen Administration	Arterial Oxygen Content, % by Volume	Oxygen Capacity, % by Volume	Arterial Oxygen Saturation, %	Arterial Carbon Dioxid Content, % by Volume	Cyanosis	Pulse Rate	Respiration Rate	Temperature	Remarks
1	48 yr.	Lobar pneumonia; chronic alcoholism; drug addict; bilateral inguinal hernia	1/29/25	None.....	10.6	14.5	73.1	41.2	+++	128	60	103.0	Marked dyspnea; shallow breathing; pain in chest
			1/30/25	Nasal catheter, 24 hours	9.4	13.9	67.6	42.5	+++	126	62	104.0	Marked dyspnea; shallow breathing; prostration; delirium
			1/31/25	Chamber, 40% oxygen	11.9	13.9	85.5	46.5	+	120	50	103.0	After first four hours in chamber, pulse dropped to 112, respiration 48
			2/ 2/25	Chamber, 50% oxygen	—	—	—	—	0	105	44	100.0	Dyspnea much better; delirium tremens; taken out of chamber
			2/24/25	None.....	15.1	15.4	98.0	46.2	0	78	20	98.6	Convalescent; recovered
2	60 yr.	Lobar pneumonia; general arteriosclerosis	12/22/24	Nasal catheter, 24 hours	14.7	17.9	82.0	29.0	++	100	40	102.0	Marked dyspnea; very feeble and weak; put in oxygen chamber
			12/23/24	Chamber, 40% oxygen	14.8	16.4	90.3	30.0	0	80	32	98.6	Dyspnea much better; still very weak
			12/24/24	Chamber, 40% oxygen	—	—	—	—	0	92	38	100.0	Marked weakness; dyspnea increasing
			12/24/25	None for 3 hr..	11.0	15.0	73.4	29.0	+++	120	58	103.0	Dyspnea and weakness excessive; appeared hopelessly ill with new consolidation
			12/26/24	Chamber, 40% oxygen	13.5	15.0	90.0	31.0	0	110	48	102.5	Dyspnea better; still very weak
			12/29/24	Chamber, 40% oxygen	—	—	—	—	0	82	28	99.2	Gradual improvement last three days; taken out of chamber
			1/ 9/25	None.....	12.8	13.1	97.6	42.3	0	80	22	98.6	Convalescent; recovered
3	38 yr.	Lobar pneumonia; acute appendicitis; appendectomy	3/ 5/25	None for 2 hr..	12.1	16.4	73.8	47.2	++	130	50	103.0	Marked dyspnea and restlessness; nosepiece used for two previous days
			3/ 5/25	Nasal catheter, 1 hour	11.7	17.1	68.5	46.8	+++	140	54	103.0	Dyspnea excessive; gurgling breathing; profuse perspiration
			3/ 6/25	Chamber, 50% oxygen	15.5	17.2	90.2	51.5	0	88	32	100.4	Dyspnea much better; marked general improvement
			3/ 7/25	Chamber, 50% oxygen	—	—	—	—	0	80	30	100.0	Comfortable but weak; taken out of chamber; recovered
4	51 yr.	Lobar pneumonia; pulmonary edema	11/30/24	None.....	14.3	30.3	70.4	37.0	++++	140	30	103.8	Gurgling respiration; very toxic
			12/ 1/24	Nasal catheter, 5 hours	15.5	19.8	78.2	37.0	++++	145	36	102.4	Gurgling respiration; comatose
			12/ 1/24	Chamber, 45% oxygen	—	—	—	—	++	145	38	102.4	Died four hours later; circulatory failure

TABLE 5.—*Effect of Oxygen Treatment on Arterial Blood Gases and Clinical Condition in Sixteen Cases of Pneumonia—Continued*

Case	Age	Diagnosis	Date	Oxygen Administration	Arterial Oxygen Content, % by Volume	Oxygen Capacity, % by Volume	Arterial Oxygen Saturation, %	Arterial Carbon Dioxid Content, % by Volume	Cyanosis	Pulse Rate	Respiration Rate	Temperature	Remarks
5	....	Acute tuberculosis; pneumonia; chronic pulmonary tuberculosis	12/ 6/24	None.....	14.5	16.0	90.6	39.0	+	106	38	104.2	Moderate dyspnea; face pale
			12/ 7/24	Nasal catheter, 18 hours	14.1	16.0	88.2	37.0	+	106	38	104.4	Unchanged; put in oxygen chamber
			12/ 8/24	Chamber, 40% oxygen	15.0	16.0	93.8	42.5	0	94	34	104.0	Face and ears pink; moderate dyspnea
			12/ 9/24	None for 4 hr..	12.7	15.7	81.0	43.4	++	98	36	103.0	Face pale; dyspnea increased
			12/10/24	Chamber, 40% oxygen	—	—	—	—	0	92	34	103.0	Face pink; tuberculosis bacillus found in sputum
			12/12/24	None.....	11.7	14.6	80.2	40.0	++	96	32	104.0	Face pale; moderate dyspnea
			12/12/24	Nasal catheter	—	—	—	—	++	96	32	104.0	Unchanged
			1/18/25	None.....	8.8	9.8	89.8	54.6	+	110	24	102.0	Tuberculosis in right upper and right lower lobes, recovered as chronic tuberculosis
6	16 mo.	Lobar pneumonia; croup	2/ 9/25	Nasal catheter	—	—	—	—	++++	168	76	103.6	Dyspnea intense; face dusky
			2/ 9/25	Chamber, oxygen, 40%	—	—	—	—	+	144	56	104.0	After oxygen for three hours, pulse readily palpable
			2/10/25	Chamber, oxygen, 40%	—	—	—	—	+	134	50	103.6	Dyspnea less marked; restlessness diminished
			2/15/25	Chamber, oxygen, 40%	—	—	—	—	0	104	32	100.0	Dyspnea slight; removed from chamber; recovered
7	7 yr.	Lobar pneumonia	2/10/24	None.....	—	—	—	—	+++	145	50	104.0	Face had a grayish pallor; marked dyspnea
			2/10/24	Chamber, oxygen, 40%	—	—	—	—	0	120	38	103.6	After oxygen for four hours, dyspnea obviously diminished
			2/11/24	Chamber, oxygen, 40%	—	—	—	—	0	90	24	99.0	Crisis during night; removed from chamber; recovered
8	27 yr.	Lobar pneumonia; typhoid fever	11/24/24	None.....	—	—	—	—	++++	120	40	102.5	Marked prostration, dyspnea and weakness
			11/25/24	Nasal catheter, 16 hours	14.0	16.7	83.8	45.0	+++	118	38	102.8	Unchanged except for slight improvement in color
			11/26/24	Rebreathing apparatus	14.8	15.4	96.1	45.0	0	110	30	102.4	Dyspnea and color much better
			11/28/24	Rebreathing apparatus	—	—	—	—	0	106	30	103.0	Oxygen stopped; recovery from pneumonia and typhoid

9	70 yr.	Lobar pneumonia; pulmonary edema; general arterio-sclerosis; senility	1/19/25	None.....	13.0	15.7	82.8	38.0	++	116	35	103 5	Moderately dyspneic; feeble
			1/20/25	Nasal catheter, 12 hours	12.1	16.5	73.5	42.0	++++	120	45	102.8	Increased dyspnea; gurgling respiration
			1/20/25	Rebreathing apparatus, 3hr.	13.8	16.4	84.2	43.0	++	124	30	102.0	Gurgling respiration continued; died
10	35 yr.	Lobar pneumonia	2/ 9/25	None.....	13.0	15.4	84.5	40.4	++	120	35	104.4	Dyspnea slight; apathetic; jaundiced
			2/10/25	Nasal catheter, 24 hours	14.2	17.1	83.0	43.6	++	120	35	104.5	Unchanged
			2/11/25	Rebreathing apparatus	15.7	17.5	89.8	44.0	+	120	30	104.2	More toxic in appearance
			2/16/25	Rebreathing apparatus	18.0	18.3	98.4	46.7	0	112	35	104.0	Irrational; otherwise unchanged; died
11	24 yr.	Lobar pneumonia; empyema	2/21/25	None.....	12.9	15.7	82.2	49.5	++	112	40	103.5	Dyspnea slight; moderate prostration
			2/21/25	Nasal catheter, 5 hours	13.8	15.7	87.9	52.0	+	100	38	103.8	Unchanged
			2/22/25	Rebreathing apparatus	12.7	14.1	90.1	52.0	0	100	34	103.5	Unchanged
			3/16/25	None.....	14.0	14.5	96.5	46.1	0	90	20	98.6	Recovered after empyema operation
12	62 yr.	Lobar pneumonia	12/29/24	None.....	11.4	14.0	81.5	37.0	+++	112	40	103.0	Dyspnea moderate
			12/29/24	Nasal catheter	12.0	14.0	85.7	37.0	++	112	40	103.0	Unchanged dyspnea; color better
			1/25/25	None.....	13.8	14.2	97.2	46.5	0	82	22	98.6	Convalescent; recovered
13	17 yr.	Lobar pneumonia	3/13/25	None.....	14.4	16.8	85.8	44.1	+	130	35	104.5	Moderate dyspnea; serum treated
			3/14/25	Nasal catheter	13.3	14.8	89.9	46.6	0	110	35	104.0	Dyspnea a little less; recovered
14	17 yr.	Lobar pneumonia	3/18/25	Nasal catheter	12.5	19.8	63.2	55.8	++++	120	28	102.4	Delirious; very restless and toxic; nails very blue
			3/19/25	Chamber, oxygen, 50%	17.0	19.0	89.5	53.3	+	110	24	102.0	Quiet; no dyspnea
			3/22/25	Chamber, oxygen, 50%	—	—	—	—	0	100	24	100.0	Removed from chamber; recovered
15	62 yr.	Lobar pneumonia; arteriosclerosis; hypertension	3/29/25	None.....	12.2	16.8	72.6	42.5	++++	110	32	101.6	Marked prostration; nails very blue
			3/30/25	Chamber, oxygen, 50%	15.4	16.9	91.2	49.0	0	100	20	99.6	Marked prostration; nails pale; died
16	40 yr.	Lobar pneumonia	4/ 1/25	None.....	13.8	16.8	82.1	47.4	+++	130	36	103.0	Marked prostration
			4/ 2/25	Chamber, oxygen, 50%	15.4	16.9	91.2	49.5	0	130	32	103.0	Marked prostration and weakness; died

REPORT OF CASES

CASE 1.—A colored man, aged 48, became sick four days before admission with chills and fever, pain in the side, bloody expectoration and difficult breathing. The previous history disclosed that he was a chronic alcoholic and morphin addict. Physical examination showed a man of middle age sitting propped up in bed, with great dyspnea, the rate being 60 and the breathing very shallow. Lung signs indicated consolidation of the right middle lobe and the right lower lobe. The abdomen was distended, the liver palpably enlarged, and there was bilateral inguinal hernia. The white blood cells totaled 19,700, polymorphonuclears, 85 per cent. A sputum culture yielded pneumococcus Type II. A blood culture was sterile.

The arterial oxygen saturation on admission was 73.1 per cent. Oxygen was administered for twenty-four hours by nasal catheter at approximately 1 liter per minute. The dyspnea, however, appeared even worse, and the patient became delirious. The oxygen saturation of the arterial blood with the catheter in situ was 67.6 per cent. He was put in the chamber on the fifth day of the disease, with the oxygen concentration kept at 40 per cent. In four hours his pulse had dropped from 128 to 112 and the respiratory rate from 62 to 48. The dyspnea was obviously diminished. On the following day his arterial oxygen saturation was 85.5 per cent in the chamber. He remained in the chamber in all five days, when his convalescence seemed assured. Recovery followed, complicated by delirium tremens.

In this patient a grave prognosis appeared justified by the history of chronic alcoholism and morphinism, the marked prostration and delirium, and the excessive dyspnea of the rapid, shallow type. Oxygen by nasal catheter did not affect the clinical condition or the oxygen content of the arterial blood. As a result of breathing 40 per cent. oxygen, a drop in pulse and respiration rate occurred independent of any fall in temperature, with an increase in arterial oxygen saturation. It is to be noted that the arterial oxygen saturation was not brought to the normal level although it was substantially elevated. Perhaps in this case a concentration of 60 per cent. in the chamber might have produced even better results.

CASE 2.—A man, aged 60, following a cold became ill with cough, fever and difficulty in breathing. The course became progressively worse for five days; then the patient entered the hospital. Physical examination showed an old feeble negro sitting propped up in bed, breathing rapidly and with obvious distress. The lung signs indicated consolidation of the right lower lobe and the left lower lobe. The abdomen was distended, and the liver palpably enlarged. The white blood cells totaled 16,500; polymorphonuclears, 92 per cent.; red blood cells, 3,690,000, and hemoglobin, 70 per cent. The urine had a faint trace of albumin with granular casts. A sputum culture yielded pneumococcus Type IV. A blood culture was sterile.

During the next five days the patient's dyspnea and weakness increased. Oxygen was administered by nasal catheter, approximately 1 liter per minute. Arterial oxygen saturation on the tenth day of illness was 82 per cent. with the catheter in situ. The patient was then placed in the chamber, and the oxygen concentration kept at 40 per cent. In three hours the pulse dropped from 100 to 88, without a fall in temperature or respiratory rate. On the following day the patient seemed better. The arterial oxygen saturation was 90.3 per cent. The temperature remained down for one day and again rose with the recurrence of severe prostration, dyspnea and weakness. On the fifteenth day of the

disease, the pulse which had previously been good, became thready and intermittent and the rate 120. Three unsuccessful exploratory chest punctures were made to look for a possible empyema, suggested by the clinical course and the roentgenograms. The patient seemed hopelessly ill, respirations having mounted to 58. The arterial oxygen saturation out of the chamber was 73 per cent. That night the oxygen concentration of the chamber was raised to 45 per cent. On the following day, with persistent temperature, there was considerable improvement in the general appearance, as well as a fall in pulse and respiratory rate; arterial oxygen saturation was 90 per cent. Two days later the patient had improved markedly and was removed from the chamber with a normal temperature, a pulse rate of 86 and respiratory rate of 28.

This patient seemed desperately ill when oxygen treatment was begun. His prostration and weakness throughout the entire course of illness was marked. It appeared that the seven days that he spent in the chamber tided him over until he developed sufficient antibody. When out of the chamber on the fifteenth day for exploratory chest punctures and for roentgen-ray examination of the chest, his dyspnea was at its worst. Several hours later, breathing 45 per cent. oxygen, there was noticeable improvement in the breathing and later in the night in the pulse. Oxygen by nasal catheter did not seem to be of much help, the arterial oxygen saturation being 82 per cent. with the catheter in situ, and on two occasions being 90 per cent. in the chamber. It is of considerable interest that the arterial carbon dioxid content rose from 29 per cent. by volume to 42.3 per cent. by volume during convalescence; this suggests a lowered alkaline reserve during the acute stage of the illness.

CASE 3.—A man, aged 38, two and a half weeks after an operation for removal of the appendix, developed a cough, rusty sputum and a temperature of 104. Physical examination showed a thin, adult man, in moderate dyspnea and slightly cyanotic. The lung signs indicated consolidation of the right lower lobe. White blood cells totaled 15,800; polymorphonuclears, 90 per cent. The sputum contained no pneumococci. A blood culture was sterile. On the fifth day of the disease dyspnea, cyanosis and prostration had increased and oxygen was given with the rebreathing apparatus, using the nose-piece. A second sputum examination revealed pneumococcus Type I, and a blood culture was positive for pneumococcus Type I. Serum treatment was begun. On the sixth day consolidation spread to the left lower lobe, the right middle lobe and the right upper lobe, with no signs of resolution in the right lower lobe. The patient grew rapidly worse. He objected to the nose-piece and oxygen by this method was discontinued. One hour later the arterial oxygen saturation was 73.8 per cent., and gurgling respiration had developed. The use of a nasal catheter for one hour at 2 liters per minute resulted in no perceptible change, the arterial oxygen saturation with the catheter in situ being 68.5 per cent. The patient was then put in an oxygen tent, the concentration of oxygen being kept at 50 per cent. Four hours later decided improvement was manifest. His rebreathing was easier; the nails were somewhat pink; the pulse had slowed, and there was no gurgling in the throat. Serum treatment was resumed and on the following day the temperature began to fall. The arterial oxygen saturation was 90.2 per cent. The patient was kept in the tent in all three days, when he was removed convalescent. Subsequently, he was operated on for empyema.

On the sixth day of disease this patient had a positive blood culture, with the left upper lobe uninvolved by consolidation. The arterial oxygen saturation at its lowest was 68.5 per cent. He would tolerate no use of any portable oxygen apparatus. The nasal catheter did not raise the oxygen content of the arterial blood. The inhalation of 50 per cent. oxygen in the tent increased his arterial oxygen saturation to 90.2 per cent. and was followed by unmistakable clinical improvement. During his residence in the oxygen tent, massive serum treatment was followed by a sterile blood culture and the crisis. It seemed probable that oxygen treatment tided the patient to a period when a specific immunity was established with the help of serum administration.

CASE 4.—A man, aged 51, six days before admission became sick with chills, fever and cough. Physical examination showed a well developed man, intensely cyanotic and dyspneic, with loud, gurgling respiration. The lung signs indicated consolidation of the left lower and the right upper lobes. Heart sounds were inaudible. The white blood cells totaled 20,800; polymorphonuclears, 93 per cent. A sputum culture yielded pneumococcus Type III, and a blood culture was positive for pneumococcus Type III. Oxygen was administered through a nasal catheter at about 1.5 liters per minute, with slight lessening of cyanosis and increase of arterial oxygen saturation from 70.4 to 78.2 per cent. The pulse became thready and intermittent. After four hours of catheter oxygen treatment, he was put in the oxygen chamber, which was kept at 45 per cent. oxygen. For a short while cyanosis perceptibly diminished, but subsequently became worse as the pulse became impalpable, the cyanosis then being largely due to a venous anoxemia. The patient died four hours later of circulatory failure.

In this patient, a man of 51 years, edema of the lungs occurred on the sixth day of the disease with the presence of pneumococcus Type III in the blood stream. Circulatory failure was imminent when he was put in the tent. He made no response to oxygen treatment.

CASE 5.—A man, aged 19, following a cold had a severe chill and soon after cough, pain in the side and blood streaked sputum. The symptoms persisted for ten days, when he entered the hospital. Physical examination showed a young, well developed man with moderate dyspnea and slight cyanosis of the nail beds. The lung signs indicated consolidation of the right lower lobe, the right middle and the right upper lobes. The white blood cells totaled 11,100; polymorphonuclears, 84 per cent. A sputum examination revealed pneumococcus Type IV; a blood culture was sterile.

On the third day after admission, the arterial oxygen saturation was 92.5 per cent. Oxygen was administered by a nasal catheter at approximately 1 liter per minute for twenty-four hours, at which time the arterial oxygen was 88.2 per cent. On the next day in the tent, the oxygen concentration was at 40 per cent., the arterial oxygen was 93.8 per cent. On the following day, the sixth day after admission, the patient was taken out of the chamber for four hours, at the end of which time considerable cyanosis had developed and the arterial oxygen had fallen to 81 per cent. On the seventh day in the tent cyanosis cleared, and on the eighth day out of the tent cyanosis returned. A nasal catheter at 1 liter per minute did not change the cyanosis. On the sixth day of disease, tubercle bacilli were found in the sputum. The patient was subsequently transferred to the roof, where treatment of chronic pulmonary tuberculosis of the right upper and the right lower lobes was carried on.

In this patient anoxemia was constantly cleared by inhalation of 40 per cent. oxygen in the tent, whereas the nasal catheter was without effect. This patient turned out to have pulmonary tuberculosis, at the onset apparently an acute tuberculous pneumonia. His respiratory embarrassment was only moderate through his illness.

CASE 6.—A girl, aged 16 months, was sick four days before admission with fever and rapid, grunting respiration. Physical examination showed a cyanotic infant breathing with great distress. The pulse was 145; respiration, 55, and temperature, 105. The lung signs indicated consolidation of the right upper lobe. The white blood cells totaled 9,500; polymorphonuclears, 70 per cent., and hemoglobin, 55 per cent. The sputum contained a streptococcus. The patient seemed to grow steadily worse and on the ninth day consolidation spread to the right middle lobe. The pulse became thready and intermittent, the rate being 168; respiration was very shallow, the rate, 74. The nail beds were deeply cyanotic; the face had a dusky grayish pallor. Oxygen by nasal catheter was attempted, but the child tossed from side to side and continually pulled it out. She was put in the oxygen chamber, the oxygen concentration being kept at 40 per cent. In three hours the pulse was fuller and stronger, the rate 144. Respiration seemed easier, the rate 56. Cyanosis was very much diminished. The patient was kept in the chamber six days when convalescence seemed assured.

This patient gave every evidence of being moribund on the ninth day of illness. The inhalation of 40 per cent. oxygen was followed by obvious improvement in subjective well-being, manifested by quietness instead of extreme restlessness, by slowing of both pulse and respiration and by the clearing of the cyanosis. She had to be kept in the tent six days before the dyspnea seemed sufficiently relieved so that she could be without oxygen. The presence of a moderately severe anemia aggravated the arterial anoxemia. The respiratory rate, 74 before oxygen treatment, was accompanied by shallow breathing, which also probably enhanced the oxygen deficiency. This was the highest respiratory rate that we have encountered.

CASE 7.—A girl, aged 7 years, following a cold in the head of one week's duration, had a chill and shortly after a severe pain in the left side. The next day she entered the hospital with a temperature of 105; pulse, 150, and respiration, 32. The lungs showed consolidation of the right lower lobe. She developed profuse bleeding from the nose. On the sixth day she appeared very prostrated. Consolidation had spread to the left lower lobe. The face was very pale with slight cyanosis of the lips and moderate cyanosis of the nail beds. The temperature was 104; the pulse, 145, and respiration varied between 44 and 45. She was put in the oxygen chamber, the oxygen concentration at 40 per cent. The cyanosis cleared and the respirations lost their grunting quality, the rate varying between 36 and 40. At the end of twenty-four hours, the crisis occurred with the subsidence of constitutional symptoms, and the patient was removed from the chamber.

In this patient a critical period of acute respiratory embarrassment on the sixth day of disease was relieved by the inhalation of 40 per cent. oxygen. The disappearance of restlessness and of the grunting quality to expiration occurred three hours after she was put in the tent.

CASE 8.—A woman, aged 27, became ill eight days before admission with malaise, headache and fever. There was no history of cough, chill or pain in the chest. Physical examination showed a thin young woman, prostrated and breathing in a rapid, shallow manner without expiratory grunt. There was slight cyanosis of the nail beds. The lung signs indicated consolidation of the right lower and the left lower lobes. The abdomen disclosed numerous rose spots. The white blood cells totaled 5,100; polymorphonuclears, 56 per cent. A blood culture grew *Bacillus typhosus*. No sputum was obtainable.

On the tenth day of disease cyanosis became deep, with extreme dyspnea and prostration. A nasal catheter for sixteen hours produced barely perceptible lessening of cyanosis. On the eleventh day oxygen was begun with the nose-piece rebreathing apparatus, the patient obtaining approximately a 60 per cent. oxygen mixture, at first continuously and later thirty minutes of each hour. Improvement was striking in four hours. She felt relieved of dyspnea; the color improved, and the general appearance of prostration visibly diminished. The arterial oxygen saturation was increased from 83.8 per cent., during catheter administration, to 96.1 per cent. during nose-piece administration. Oxygen was given through the nose-piece at intervals for three days, when acute respiratory distress was alleviated. The patient subsequently recovered from typhoid.

The masking of the symptoms of pneumonia by typhoid fever was typically observed in this patient. There was no cough, sputum, pain in the chest, expiratory grunt, or onset with chill. The period of acute respiratory distress appeared to be tided over by administration of 60 per cent. oxygen, with the nose-piece apparatus, after the nasal catheter had failed to alleviate substantially the cyanosis, the dyspnea or the arterial anoxemia. Massive consolidation was present in both lower lobes, but owing to the entire absence of sputum the organism could not be determined.

CASE 9.—A woman, aged 70, following a fall developed a pain in the left chest and a cough productive of rusty sputum. She entered the hospital on the fourth day of the disease. Physical examination showed a woman in advanced senility, moderately dyspneic and cyanotic. The lungs showed consolidation of the right lower lobe. The heart was slightly enlarged, with a systolic murmur at the apex. The white blood cells totaled 21,700; polymorphonuclears, 91 per cent. A blood culture was sterile. Sputum was not obtained. Oxygen was administered through a nasal catheter at approximately 1 liter per minute. The patient grew steadily worse with the development of moisture in her throat. The arterial oxygen saturation fell from 82.8 per cent. before the use of the catheter to 73.5 per cent. with the catheter in situ. When the nose-piece was applied with the rebreathing apparatus, the arterial oxygen saturation rose to 84.2 per cent. in three hours, without other signs of improvement. She died twenty-four hours later of circulatory failure.

In this patient, a woman in advanced senility, lobar pneumonia set in after a severe fall. Catheter oxygen treatment failed to arrest the progressive arterial anoxemia. The nose-piece rebreathing apparatus, providing approximately a 40 per cent. oxygen mixture, raised the arterial oxygen saturation from 73.5 to 84.2 per cent., still far from the normal level. However, no improvement in the clinical condition was apparent from the oxygen treatment.

CASE 10.—A man, aged 55, following a head cold was suddenly seized with a chill, pain in the right side and cough four days prior to admission. Physical examination showed a well developed man acutely ill, in considerable prostration, jaundiced, slightly cyanotic, and moderately dyspneic. The lung signs indicated consolidation of the right upper, the right lower and the right middle lobes. A sputum examination showed pneumococcus Type IV. A blood culture was sterile. The white blood cells totaled 13,000; polymorphonuclears, 82 per cent. Oxygen was administered by nasal catheter at 1 liter per minute for twenty-four hours, the arterial oxygen saturation changing from 84.5 to 83 per cent. With the nose-piece rebreathing apparatus, the arterial oxygen saturation was raised to 89.8 per cent. Oxygen was administered for eight days by the nose-piece rebreathing apparatus for from twenty to thirty minutes of each hour. At the end of eight days the temperature gradually fell to normal. When convalescence seemed assured the patient developed a recurrent infection and died a month later of a pneumococcus Type IV bacteremia. The focus was not determined.

In this patient oxygen lack was at no time severe. The nasal catheter failed to elevate the arterial oxygen saturation and the rebreathing apparatus, providing about 40 per cent. oxygen, increased it only moderately. No effect was observed in the clinical condition as a result of oxygen treatment.

CASE 11.—A woman, aged 24, was suddenly seized with a chill, followed by pain in the left side of the chest and cough. On the sixth day of illness, she also developed a pain in the right side of the chest, and entered the hospital. Physical examination showed a poorly nourished young woman, moderately dyspneic and slightly cyanotic. The lung signs indicated consolidation of the right lower and the left lower lobes. The white blood cells totaled 19,200; polymorphonuclears, 91 per cent. The sputum contained a hemolytic streptococcus.

The arterial oxygen saturation was 82.2 per cent. Oxygen was administered by a nasal catheter for five hours at 2 liters per minute, at which time arterial oxygen saturation was raised to 87.9 per cent. From this time on the rebreathing apparatus was used, the patient breathing through the nose-piece. On the following day the arterial oxygen saturation was 90.1 per cent. during administration through the nose-piece. Thoracotomy was subsequently performed for empyema of the left pleural cavity. The patient made a good recovery.

The nasal catheter administration at 2 liters of oxygen per minute elevated the arterial oxygen saturation from 82.2 to 87.9 per cent. After inhalation of 50 per cent. oxygen through a nose-piece rebreathing apparatus, the arterial oxygen saturation was 90.1 per cent. Since the catheter here furnished approximately 30 per cent. oxygen in the inspired air, it is seen that a measurable improvement may result from this concentration. The patient did not appear severely ill at any time.

CASE 12.—A man, aged 62, two days before admission developed pain in the chest, fever and cough. Physical examination showed a well developed man, moderately dyspneic and cyanotic. The lung signs indicated consolidation of the right upper and the right middle lobes. The white blood cells totaled 17,200; polymorphonuclears, 86 per cent. Sputum examination showed pneumococcus Type IV. A blood culture was sterile.

Oxygen through a nasal catheter was administered on the sixth day of illness, with slight improvement in the color and increase of the arterial

saturation from 81.5 to 85.7 per cent. Catheter oxygen treatment was continued until convalescence.

In this patient administration of oxygen by catheter at a rate of 2 liters of oxygen a minute, furnishing approximately 30 per cent. oxygen in the inspired air, caused a slight increase in arterial oxygen saturation, from 81.5 to 85.7 per cent., still 10 per cent. below the normal value.

CASE 13.—A boy, aged 17 years, seventeen hours before admission was seized with a shaking chill, pain in the left side of the chest and had bloody sputum. Physical examination showed a well developed boy, somewhat dyspneic and slightly cyanotic. The lungs sign indicated consolidation of the left lower lobes. The white blood cells totaled 24,200; polymorphonuclears, 90 per cent. Sputum examination showed penumococcus Type I. On the third day serum treatment was begun. Oxygen was administered by nasal catheter at 2 liters per minute, increasing the arterial oxygen saturation from 85.8 to 89.9 per cent.

Catheter oxygen treatment resulted in a moderate elevation of the arterial oxygen saturation. In this instance at 2 liters per minute the inspired air contained 30 per cent. oxygen. There was an uneventful recovery.

CASE 14.—A boy, aged 14 years, was suddenly seized with a severe chill, followed by a sharp pain in the left side. On the following day cough began, with blood streaked sputum, and the patient entered the hospital. Physical examination showed a prostrated boy with little dyspnea and slight cyanosis. The lung signs indicated consolidation of the left lower lobe. The white blood cells totaled 15,300; polymorphonuclears, 96 per cent. Sputum examination showed pneumococcus Type I. A blood culture was sterile. Serum treatment was instituted. On the fifth day consolidation extended to the right lower lobe and the patient became irrational, very toxic and cyanotic; use of a nasal catheter was attempted at 2 liters of oxygen per minute, but the patient would not tolerate it.

The arterial oxygen saturation with the nasal catheter in situ was 63.2 per cent. He was placed in an oxygen tent, the oxygen concentration being kept at 50 per cent. The cyanosis cleared; the respirations fell from 28 to 14, the pulse from 120 to 110, and the patient lost active delirium. On the following day the arterial oxygen saturation was 89.5 per cent. The patient was in the chamber four days, when convalescence was established.

In this patient an extension of consolidation on the fifth day of the disease was attended with active delirium, deep cyanosis and marked prostration. Catheter oxygen treatment was unsuccessful both in raising the oxygen content of the arterial blood and in alleviating the clinical signs of respiratory embarrassment. The inhalation of 50 per cent. oxygen in the tent was followed by an elevation of the arterial oxygen from 63.2 to 89.5 per cent.; a clearing of cyanosis; a fall in the respiratory rate from 28 to 14; a decrease in the pulse rate from 120 to 110, and a striking diminution in delirium and restlessness. Convalescence occurred after four days in the tent.

CASE 15.—A woman, aged 62, felt poorly for three days, when she developed a frequent cough, with blood streaked sputum and fever. She entered the hospital on the following day. Physical examination showed an old woman, who appeared at least 70, in slight dyspnea, without cyanosis or prostration. The lungs showed beginning consolidation of the right lower lobe. The heart was enlarged to the left, with numerous premature contractions. The systolic blood pressure was 185, the diastolic 80. The patient had general arteriosclerosis. The white blood cells totaled 21,800; polymorphonuclears, 84 per cent. Sputum examination showed pneumococcus Type III. During the next five days consolidation spread to the right upper, the right lower and the right middle lobes, and edema of the lungs began. A blood culture was positive for pneumococcus Type III.

The arterial oxygen saturation was 72.6 per cent. She was put in the oxygen tent, the oxygen concentration being kept at 50 per cent On the following day the arterial oxygen was 91.2 per cent. The respiratory rate had decreased from 36 to 20, and the pulse from 110 to 100. Edema of the lungs persisted, and the patient seemed to grow steadily weaker. On the following morning she was taken out of the tent for a short time and deep cyanosis returned, with immediate acceleration of the respiratory rate to 36. When she was replaced in 50 per cent. oxygen, the color returned and the respiratory rate slowed. The pulse rate had gradually risen during the night to 160 and at noon became impalpable, and the patient died.

This patient was in the hospital from the first day of disease. Although she gave her age as 62 she seemed at least ten years older. The invasive power of pneumococcus Type III in this instance could be watched from day to day, as consolidation involved progressively every lobe except one, with the organism present in the blood stream. The inhalation of 50 per cent. oxygen slowed her respiratory rate to 20 and brought the arterial oxygen almost to the normal level. The pulse on the first day in the tent was 100 and of good quality. The toxic appearance, however, never left her, and death occurred as a result of cardiac failure.

CASE 16.—A woman, aged 40, following a cold became acutely ill with pains in the chest, cough and fever. She entered the hospital on the third day of illness. Physical examination showed a well nourished woman, considerably prostrated, moderately dyspneic and cyanotic. The lung signs indicated consolidation of the right lower lobe. The white blood cells totaled 12,200; polymorphonuclears, 92 per cent. Sputum examination showed pneumococcus Type III. A blood culture was sterile. Two days later consolidation had spread to the right middle and the left lower lobes. Dyspnea, cyanosis and prostration were worse. The arterial oxygen saturation was 82.1 per cent.

The patient was put in an oxygen tent, the oxygen concentration being maintained at 50 per cent. The cyanosis cleared and the arterial oxygen on the following day was 91.1 per cent. The patient still appeared very toxic. The pulse remained at 130; the respiratory rate changed from 36 to 32, and edema of the lungs began. A blood culture was now positive for pneumococcus Type III. The next day the pulse rose to 156, became irregular, and the patient died.

In this patient also, pneumococcus Type III was associated with progressive advancement of consolidation and blood stream infection. Prostration was marked throughout. Although arterial oxygen was elevated no clinical benefit resulted.

COMMENT

Methods.—The tube and funnel may be dismissed as a relatively ineffective method. At the maximum rate at which oxygen may be practically administered, i. e., 2 liters a minute, the air in the nasopharynx contained 22 per cent. oxygen, corresponding approximately to 24 per cent. in the inspired air.

The nasal catheter when conscientiously employed at the rate of 1 liter per minute yielded an oxygen concentration of 25 per cent. in the nasopharyngeal air. Under certain conditions, in which 2 liters of oxygen are administered, the oxygen concentration of the nasopharyngeal air may be from 30 to 33 per cent. This involves the use of a relatively large amount of oxygen and is most practicable with high pressure oxygen.

The clinical results of catheter oxygen treatment are variable. In the mild cases a measurable increase in the arterial oxygen saturation may occur, occasionally also in the severe ones, but in none is the increase up to normal level. In patients gravely ill an arterial anoxemia frequently grew worse even during the administration of oxygen by catheter, whereas the same patients were improved by the inhalation of from 40 to 60 per cent. oxygen in the tent or by the rebreathing apparatus. A summary of the cases indicates that in four the arterial oxygen saturation was increased during catheter administration; in six it was stationary or decreased, and in eight an arterial oxygen saturation obtained during catheter treatment was increased above that value by the inhalation of 40-60 per cent. oxygen. Although the series is small it defines the limitation of the nasal catheter, or more precisely, it defines the effectiveness of the inhalation of from 25 to 30 per cent. oxygen.

These results do not indicate the maximum efficiency of catheter oxygen treatment as in some instances 1 liter of oxygen was administered instead of 2 liters in order to determine the effects of a routine use in the hospital. The catheter can usually be employed, however, under conditions that will furnish from 30 to 35 per cent. oxygen in the inspired air, a concentration that is distinctly beneficial in the treatment of mild and moderate cases of anoxemia. For the relief of severe arterial anoxemia higher concentrations are generally necessary.

The rebreathing apparatus particularly with the use of the nosepiece as described appears to be an effective method of administering oxygen, providing a 40 per cent. oxygen mixture without, in most cases, disturbing the patient. The employment of a single tube permits oxygen to be breathed through one nostril and air through the other. An administration of 1 liter of oxygen per minute into the rebreathing bag results in this method in a 40 per cent. oxygen mixture. When mouth breathing takes place, as in many moribund cases, a mouthpiece must be used.

The portable oxygen tent has worked well in securing a precise oxygen concentration, and in not having any appliance to the face. It may be readily transported and is put up in an hour without necessarily moving the patient from his bed. We have not used it in summer, and believe it would be difficult to get adequate cooling under warm conditions of the external atmosphere.

Clinical Results.—Of the ten patients treated in the tent seven recovered. The three who died all suffered from a pneumococcus Type III lobar pneumonia with pneumococcus Type III in the blood stream. Of six patients treated with the more portable apparatus, four recovered. Of the two who died one had a recurrent bacteremia a month after the acute illness. The other, a woman of 72, did not have a blood culture taken during the latter part of her illness. Thus, all of the four fatal cases that had blood cultures taken had a blood stream infection. These figures are recorded not with the idea that they have any statistical value but rather to point out the limitations of oxygen therapy. The first point brought out in this series is that the benefit of oxygen treatment may be nullified by the presence of a bacteremia.

The bacteremia due to pneumococcus Type III was associated with a progressive increase in lung consolidation and in the toxic appearance of the patient. It seemed probable that in Cases 15 and 16 oxygen treatment prolonged life but its fatal outcome appeared inevitable from the presence of a blood stream infection. In Case 3, however, a pneumococcus Type I lung involvement was associated with advancing consolidation and a blood infection of pneumococcus Type I on the sixth day of disease. The outlook in this case appeared as grave as in the foregoing cases. The improvement in the clinical condition was so marked as a result of the inhalation of oxygen as to warrant the resumption of serum treatment, which was then given in massive doses and was followed by the sterilization of the blood stream and subsequent crisis. As nearly as we can judge from sequential evidence, oxygen treatment in this instance prolonged life until the immunity factor aided by serum treatment dissipated the toxemia of the disease.

Of the ten patients treated in the tent seven recovered. Although the series is too small to have the slightest statistical value, a detailed study of six of these patients who were obviously gravely ill, reveals an unmistakable alteration in their clinical course after oxygen treatment was instituted. We may now consider some of the signs of improvement that these cases made which seemed to be related to the inhalation of from 40 to 50 per cent. oxygen. The clinical and laboratory data are summarized in Table 5.

Clinically, the patient soon after his entrance into the tent appears more comfortable, with the disappearance or diminution of cyanosis, decrease of restlessness and at times relief of dyspnea. In many

instances there is a drop in the pulse or the respiratory rate or in both. Slowing of the pulse or respiration must be dissociated as far as possible from a fall in temperature in order to ascribe the effect to the inhalation of oxygen.

In Table 6 a comparison is made between the pulse and the respiratory rate before and after increase of arterial oxygen saturation. The temperature has been added for the time these observations were made. (In this table some of the results of the cases not in the oxygen tent are included.)

TABLE 6.—*Effect of Increasing Arterial Oxygen Saturation on Pulse and Respiration Rate*

Case	Increase of Arterial Oxygen Saturation, per Cent.		Change in Pulse Rate		Change in Respiration Rate		Change in Temperature Rate	
	Before	After	Before	After	Before	After	Before	After
1	67.6	85.5	126	112	62	48	104.0	104.0
2	73.4	90.0	120	110	58	48	103.0	102.5
3	68.5	90.2	140	88	54	32	103.0	100.4
5	88.2	93.8	106	94	38	34	104.4	104.0
8	83.8	96.1	118	110	38	30	102.8	102.4
9	73.5	84.2	120	124	45	30	102.8	102.0
10	83.0	89.8	120	120	35	30	104.5	104.3
11	87.9	90.1	112	100	38	34	103.8	103.5
12	81.5	85.7	112	112	40	40	103.0	103.0
13	85.8	89.9	130	120	35	35	104.5	104.0
14	63.2	89.5	120	110	28	24	102.4	102.0
15	72.6	91.2	110	100	36	20	101.6	99.6
16	82.1	91.2	130	130	36	32	103.0	103.0

It is seen that in six cases definite slowing of the pulse and in six cases, not necessarily the same, slowing of the respiratory rate occurred unexplained by a fall in temperature. Thus, in Case 1 the pulse dropped from 126 to 112, and the respiratory rate from 62 to 48. In the foregoing case histories, instances are found in which the fall in the respiratory rate and the pulse rate took place during several hours immediately after inhalation of from 40 to 50 per cent. oxygen, viz., Cases 1, 2, 3, 6 and 14, instances in which improvement of respiration and pulse was definitely related to the inhalation of an oxygen rich atmosphere. It is to be noted that in no instance did the pulse rate approach normal, a fall of from 8 to 14 beats being the usual drop in those in which slowing occurred at all. However, in the infant in this series the pulse before oxygen treatment was 168, of very poor quality and at times intermittent, and three hours later in 45 per cent. oxygen was 144 and of good quality.

The slowing of the respiration when it occurs is likewise apt to be between 6 and 14 per minute, with from 8 to 10 a fair average. As a rule the slowing of the respiratory rate does not approach normal, but two cases were so reduced, Cases 14 and 15. In the first, respirations dropped from 28 to 14, and in the second from 36 to 20.

From the data obtained in this series and from earlier investigations it may be said that the slowing of the pulse is of more frequent occurrence as a result of oxygen inhalation than slowing of the respiratory rate, and occurs in more than half the cases. It may be of small degree, such as from 4 to 8 beats a minute, and may be ascertained only by careful counts before oxygen inhalation and at frequent intervals during the ensuing several hours. The four hour temperature chart may not show these differences. In severely anoxemic cases, as has been pointed out, a more striking drop in pulse rate may be expected.

The slowing of the respiratory rate as a result of oxygen inhalation appears to occur approximately in half the cases, being more striking and more frequent in the severe cases. The relief of dyspnea is apt to be associated with the decreased rate rather than a decrease in tidal air.[8] This was clearly shown in a case of Binger [20] in which the pulmonary ventilation was determined when the patient was in the oxygen chamber one day and exposed to room air the following day.

It may be mentioned that in all the cases studied an increase in arterial oxygen saturation was effected by the inhalation of from 40 to 60 per cent. oxygen but that in only two cases was the arterial oxygen brought to the normal level. In the severe cases of arterial anoxemia, from 89 to 91 per cent. saturation was the usual maximum achieved by oxygen treatment. Most of these cases represented the severest types of anoxemia seen in routine ward services and were selected for this reason. Substantial elevation of the oxygen content was nevertheless produced. These observations are in accord with earlier investigations.[1]

It is of some interest to examine the determinations of the arterial carbon dioxid content in these cases. The average for normal persons Peters, Barr and Rule [21] found to be 49.3 per cent. by volume. Of the fourteen cases in this series five were above 45 per cent. by volume, five between 40 and 45 per cent. by volume, and five below 40 per cent. by volume. In other words, in five of fourteen patients a distinct decrease in the carbon dioxid content of the arterial blood was present. In one case only was this severe, Case 2, in which the arterial carbon dioxid content was 29 per cent. by volume. As convalescence was reached the carbon dioxid content manifested a distinct tendency to rise toward normal; thus, in Case 1, from 41.2 to 46.2 per cent. by volume; in Case 2, from 29 per cent. by volume to 42.3 per cent. by volume; in

20. Binger, C. A. L.; Hastings, A. B., and Neill, J. M.: Edema Associated with Moderate Bicarbonate Administration During Convalescence from Pneumonia, Arch. Int. Med. **31**:145 (Jan.) 1923.

21. Peters, J. P.; Barr, D. P., and Rule, F. D.: Carbon Dioxid Absorption Curve and Carbon Dioxid Tension of Blood of Normal Resting Individuals, J. Biol. Chem. **45**:489 (Feb.) 1921.

Case 5, from 39 per cent. by volume to 54.6 per cent. by volume, and in Case 12 from 37 per cent. by volume to 46.5 per cent. by volume.

It is beyond the scope of this article to review the question of acidosis in pneumonia. A decrease in the fixed alkali of the blood as well as a lowered blood p_H has been observed by some investigators, whereas others have found only normal values. Recent experiments on animals suggest that the cause of these discordant results may lie in the presence or absence of severe anoxemia. When pigs are subjected to relatively mild anoxemia, there is a fall in the blood carbon dioxid capacity with a slight alkalosis; with severe anoxemia the reduction in blood carbon dioxid is accompanied by a decided lowering of the p_H.[22] In addition there is a marked increase in the excretion of organic acids in the urine. An acidosis, as evidenced by a fall in carbon dioxid capacity and arterial blood p_H, has been described in experimental pneumonia in dogs, "due chiefly to the effects of an anoxic anoxemia."[23] The patients in this study as well as in that previously reported[24] were generally selected because of the presence of severe arterial anoxemia.

SUMMARY AND CONCLUSIONS

1. Experiments were conducted on the efficacy of certain methods of administering oxygen by analyzing the oxygen concentration of the nasopharyngeal air, by calculating the oxygen concentration of the inspired air, and by the arterial oxygen saturation before and after treatment.

2. The tube and funnel method at its maximum efficiency raises the air in the nasopharynx to 22 per cent., and may be considered almost useless as a therapeutic agent. With oxygen administered at 2 liters per minute, the inspired air has an oxygen concentration of approximately 24 per cent.

3. The nasal catheter may vary in its effectiveness to the extent that the nasopharyngeal air may contain between 22 and 35 per cent. oxygen, depending largely on the rate of administration of oxygen from the tank. At 1 liter per minute the inspired air contains approximately 25 per cent. oxygen. Under special conditions, including a flow of 2 liters of oxygen per minute, the inspired air contains approximately 30 per cent. oxygen. The advantages of high pressure oxygen for this purpose were pointed out.

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22. Brunquist, E. H.; Schneller, E. J., and Loevenhart, A. S.: The Effects of Anoxemia on Nitrogen Metabolism, J. Biol. Chem. **62**:93 (Nov.) 1924.

23. Leake, C. D.; Vickers, J. L., and Brown, T. K.: Blood Reaction in Experimental Pneumonia, J. Exper. Med. **39**:393 (March) 1924.

24. Barach, A. L.; Means, J. H., and Woodwell, M.: The Hydrogen Ion Concentration and Bicarbonate Level of the Blood in Pneumonia, J. Biol. Chem. **50**:413 (Feb.) 1922.

When catheter oxygen treatment is carried out at its maximum efficiency there is apt to be considerable increase in the oxygen saturation of the arterial blood, particularly in the mild and moderate cases of oxygen want. For the relief of severe arterial anoxemia higher concentrations of oxygen than this method affords appear to be necessary.

4. The rebreathing apparatus with the use of a specially constructed glass nose-piece is the most efficient of the easily portable types of apparatus and in most cases causes little discomfort to the patient. The mouthpiece is used at times when mouth breathing is present. With the nose-piece rebreathing apparatus 1 liter of oxygen per minute provides a 40 per cent. oxygen mixture in the inspired air. Observations on the arterial blood confirm the effectiveness of the method.

5. The portable oxygen tent as devised by Binger and myself was used in the majority of cases treated. It secured an oxygen rich atmosphere capable of regulation at the precise concentration desired. It accomplished adequate removal of carbon dioxid, moisture and heat, and was comfortable for the patient to live in. In warm weather the tent was not used because of difficulty in cooling under these conditions.

6. Of ten cases treated in the oxygen tent seven recovered. The three patients who died all had pneumococcus Type III in their sputum, with pneumococcus Type III bacteremia. Of the six patients treated with a portable apparatus four recovered. Of the two who died one developed a bacteremia late in convalescence. These results indicate that the grave prognosis of a persistent bacteremia in lobar pneumonia is unaltered by the administration of oxygen.

7. All the patients except one who were treated in the oxygen tent were gravely ill. The clinical signs of improvement that were especially apt to follow inhalation of from 40 to 60 per cent. oxygen were: (1) clearing of cyanosis; (2) partial relief of dyspnea; (3) diminution of restlessness and promotion of sleep; (4) slowing of the respiratory rate and the pulse rate, more constant in the severe cases, and (5) a tendency to lessened delirium.

8. The arterial oxygen saturation was increased in all the tested cases. In severe arterial anoxemia the inhalation of 40-60 per cent. oxygen raised the arterial oxygen saturation substantially but not to the normal level.

9. The arterial carbon dioxid content was lowered in five of fourteen cases. This decrease was severe in only one patient.

10. The value of oxygen treatment is felt to be supportive and not curative. In severe dyspnea with cyanosis, oxygen treatment has appeared to prolong life until such a time as the immunity mechanism was able to accomplish recovery. In this series six patients seemed to be aided in this manner.

GASTRIC SECRETION IN EXPERIMENTAL BERIBERI IN THE DOG*

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Clinically, a decreased gastric acidity has been reported a number of times in severe cases of beriberi. Experimentally, both a decreased acidity as well as a diminished secretion have been observed in dogs kept on a beriberi producing diet. Myadere, however, reported that in such an experimental dog the gastric glands could still be stimulated to a normal secretion by alcohol taken by mouth.

The purpose of the studies I am reporting on was, first, to confirm the change in the volume and character of the gastric secretion in experimental beriberi; second, to confirm the changes therein during a recovery from beriberi as a result of a normal or control diet; third, to determine the change, if any, in the response of the gastric secretion to such stimulants as histamin and gastrin as compared with a food stimulus; fourth, to prove that the antineuritic water soluble B is not a gastric secretagogue, and, fifth, to prove that the addition of this antineuritic vitamin to an otherwise beriberi producing diet keeps the dog in good condition.

The experimental procedure was to prepare Pawlow pouch dogs and to study the gastric secretion in these animals before and during the production of beriberi as affected by food, histamin, gastrin and Harris yeast vitamin. The beriberi producing diet was the same as the control diet with the exception that the former was autoclaved after the addition of sodium carbonate. To neutralize the base thus formed in the autoclaving process the mixture was slightly acidified with hydrochloric acid before feeding. An amount of salt equivalent to the amount thus formed was added to the control diet.

In Tables 1 and 2 are given the results showing the effect of the diet, autoclaved in an alkaline condition, on the gastric secretion of Pawlow dogs. It required from thirty-one to thirty-three days to bring about severe symptoms of beriberi, but several weeks before this a decreased secretion or a lowered acidity in gastric juice, or both, is observed.

Table 3 shows that the same diet produced beriberi in thirty days with a much earlier loss in secretion and acidity of gastric juice. This animal was brought back to a normal condition on the control diet in forty-one days, and after continuing on this for another thirty-five days was then again placed on the diet autoclaved without the addition of sodium carbonate. Although the animal had already been in the poly-

* From the Department of Physiological Chemistry, University of Chicago.

TABLE 1.—*Effect of Diet Autoclaved with Alkali (20 C.c. of 10 Per Cent. Sodium Carbonate Per 400 Gm. Food) on Gastric Secretion of Dog (Experiment 2)*

Date	Volume in C.c. for Four Hours	Average Free Acidity, per Cent. Hydrochloric Acid	Average Total Acidity, per Cent. Hydrochloric Acid	Remarks
1/19/24.....	20.0	0.27	0.36	Fresh diet
1/20/24.....	13.4	0.13	0.28	Fresh diet
1/23/24.....	18.2	0.29	0.37	Fresh diet
1/26/24.....	15.5	0.18	0.31	Autoclaved diet first day
1/29/24.....	18.4	0.18	0.28	Autoclaved diet fourth day
2/ 2/24.....	13.0	0.06	0.16	Autoclaved diet eighth day
2/ 3/24.....	20.2	0.17	0.25	Autoclaved diet ninth day
2/ 4/24.....	13.0	0.13	0.22	Autoclaved diet tenth day
2/ 5/24.....	16.4	0.22	0.28	Autoclaved diet eleventh day
2/ 9/24.....	8.4	0.04	0.11	Autoclaved diet fifteenth day
2/12/24.....	8.3	0.11	0.18	Autoclaved diet eighteenth day
2/16/24 (5 hours)	10.2	0.12	0.18	Autoclaved diet twenty-second day
2/18/24 (5 hours)	6.4	0	0.08	Autoclaved diet twenty-fourth day
2/23/24 (6 hours)	18.8	0.14	0.20	Autoclaved diet twenty-ninth day
2/24/24 (5 hours)	12.9	0.10	0.17	Autoclaved diet thirtieth day
2/25/24 (5 hours)	11.5	0.17	0.28	Autoclaved diet thirty-first day
2/29/24.....	....	....	....	Very weak; died in afternoon

TABLE 2.—*Effect of Diet Autoclaved with Alkali on Gastric Secretion of Dog (Experiment 27)*

Date	Volume in C.c. for Five Hours	Average Free Acidity, per Cent. Hydrochloric Acid	Average Total Acidity, per Cent. Hydrochloric Acid	Remarks
3/ 1/24.....	12.3	0.17	0.23	Fresh diet
3/ 2/24.....	20.9	0.23	0.28	Fresh diet
3/ 3/24.....	18.5	0.27	0.32	Fresh diet
3/ 4/24.....	20.0	0.25	0.29	Fresh diet
3/ 9/24.....	13.5	0.24	0.30	Fresh diet
3/16/24.....	14.7	0.21	0.25	Autoclaved diet second day
3/19/24.....	16.0	0.32	0.39	Autoclaved diet fifth day
3/22/24.....	16.4	0.35	0.41	Autoclaved diet eighth day
3/25/24.....	16.6	0.34	0.35	Autoclaved diet eleventh day
3/27/24.....	18.3	0.31	0.36	Autoclaved diet thirteenth day
3/31/24.....	19.0	0.26	0.30	Autoclaved diet seventeenth day
4/ 1/24.....	16.7	0.27	0.31	Autoclaved diet eighteenth day
4/ 4/24.....	13.0	0.18	0.26	Autoclaved diet twenty-first day
4/ 5/24.....	15.6	0.21	0.29	Autoclaved diet twenty-second day
4/ 6/24.....	9.7	0.13	0.19	Autoclaved diet twenty-third day
4/ 9/24 (8 hours)	9.6	0.08	0.16	Autoclaved diet twenty-sixth day
4/15/24.....	1.1	0	0	Autoclaved diet thirty-second day
4/16/24 (6 hours)	2.0	0.10	0.21	Autoclaved diet thirty-third day
4/20/24.....	....	....	....	Stiff legged and dizzy; dead thirty-seventh day

TABLE 3.—*Effect of (1) Fresh Diet, (2) a Diet Autoclaved with Alkali, (3) Fresh Diet, (4) a Diet Autoclaved with No Alkali, and (5) Fresh Diet on Gastric Secretion of Dog (Experiment 23)*

Date	Volume in C.c. for Four Hours	Average Free Acidity, per Cent. Hydrochloric Acid	Average Total Acidity, per Cent. Hydrochloric Acid	Remarks
2/ 3/24.....	36.6	0.25	0.28	Fresh diet
2/ 9/24.....	36.0	0.29	0.33	Fresh diet
2/12/24.....	36.5	0.31	0.34	Fresh diet
2/23/24.....	29.8	0.15	0.22	Autoclaved diet (alkali) eighth day
3/ 4/24.....	24.2	0.14	0.21	Autoclaved diet eighteenth day
3/10/24.....	17.2	0.06	0.16	Autoclaved diet twenty-fourth day
3/15/24.....	24.7	0.16	0.26	Autoclaved diet twenty-ninth day
3/16/24.....	25.2	0.15	0.22	Autoclaved diet thirtieth day
3/22/24.....	....	....	....	Pronounced symptoms of beriberi
3/22/24.....	11.3	0.13	0.19	Fresh diet third day
4/ 6/24.....	20.4	0.21	0.26	Fresh diet eighteenth day
4/30/24.....	27.8	0.31	0.37	Fresh diet forty-first day
5/21/24.....	24.2	0.25	0.31	Fresh diet sixty-fourth day
6/ 2/24.....	29.9	0.25	0.31	Fresh diet seventy-sixth day
6/14/24.....	14.2	0.22	0.28	Autoclaved diet (no alkali) twelfth day
6/28/24.....	15.9	0.21	0.27	Autoclaved diet twenty-sixth day
7/ 9/24.....	11.4	0.18	0.24	Autoclaved diet thirty-seventh day
7/25/24.....	11.3	0.18	0.22	Autoclaved diet fifty-third day
8/15/24.....	8.2	0.19	0.24	Autoclaved diet seventy-fourth day
8/28/24.....	12.1	0.19	0.22	Autoclaved diet eighty-seventh day
9/ 7/24.....	21.7	0.33	0.38	Autoclaved diet ninety-seventh day
9/15/24.....	....	....	....	Mild symptoms of beriberi; no appetite one hundred and fifth day
9/20/24.....	15.4	0.17	0.20	Fresh diet fifth day
9/21/24.....	16.6	0.25	0.30	Fresh diet sixth day

neuritic condition, it nevertheless required 105 days to reproduce the obvious symptoms of beriberi. The gastric secretion during this fourth experimental period fluctuated considerably both in volume and in acidity, but the tendency was on the whole toward a decreased total secretion of acid.

TABLE 4.—*Effect of Autoclaved Diet on Response to Histamine Hydrochlorid Stimulation of Gastric Secretion (Experiment 43)*

Date	Volume in C.c. First Hour	Free Acidity, per Cent. Hydrochloric Acid	Total Acidity, per Cent. Hydrochloric Acid	Remarks
7/26/24	11.5	0.37	0.46	1 mg. of histamine hydrochlorid; fresh diet
7/28/24	3.1	0.25	0.34	0.5 mg. of histamine hydrochlorid; fresh diet
7/29/24	1.0	0	0.08	0.1 mg. of histamine hydrochlorid; fresh diet, no mucus
7/30/24	1.5	0	0.05	0.1 mg. of histamine hydrochlorid; fresh diet, watery
7/31/24	1.8	0	0.06	0.1 mg. of histamine hydrochlorid; fresh diet, watery
8/ 2/24	8.0	0.20	0.35	0.4 mg. of histamine hydrochlorid; fresh diet
8/ 5/24	2.1	0	0.07	0.1 mg. of histamine hydrochlorid fourth day; autoclaved diet; mostly mucus
8/15/24	1.0	0.02	0.16	0.1 mg. of histamine hydrochlorid fourteenth day; autoclaved diet
8/21/24	1.0	0	0.05	0.1 mg. of histamine hydrochlorid twentieth day; autoclaved diet; mostly mucus
	2.0	0.06	0.16	0.15 mg. of histamine hydrochlorid twentieth day; autoclaved diet
8/22/24	5.0	0.06	0.33	0.4 mg. of histamine hydrochlorid twenty-first day; autoclaved diet
8/28/24	1.1	0.05	0.20	0.15 mg. of histamine hydrochlorid twenty-seventh day; autoclaved diet
8/29/24	4.0	0.30	0.46	0.60 mg. of histamine hydrochlorid twenteighth day; autoclaved diet
8/31/24	2.5	0.03	0.16	0.15 gm. of histamine hydrochlorid thirtieth day; autoclaved diet
9/ 1/24	1.5	0.24	0.28	0.60 mg. of histamine hydrochlorid thirty-first day; autoclaved diet
9/ 2/24	....	....	....	Died; slight symptoms of beriberi

TABLE 5.—*Effect of Autoclaved Diet on Response to Histamine Hydrochlorid Stimulation of Gastric Secretion in Dog (Experiment 48)*

Date	Volume in C.c. First Hour	Free Acidity, per Cent. Hydrochloric Acid	Total Acidity, per Cent. Hydrochloric Acid	Remarks
8/26/24	3.5	0.13	0.25	0.1 mg. of histamine hydrochlorid; fresh diet
	10.5	0.34	0.40	0.4 mg. of histamine hydrochlorid; fresh diet
8/29/24	2.5	0.10	0.18	0.05 mg. of histamine hydrochlorid; fresh diet
	4.5	0.22	0.30	0.2 mg. of histamine hydrochlorid; fresh diet
8/29/24	2.5	0	0.08	0.05 mg. of histamine hydrochlorid; fresh diet
	3.7	0.13	0.22	0.2 mg. of histamine hydrochlorid; fresh diet
9/ 6/24	3.7	0	0.04	0.05 mg. of histamine hydrochlorid; autoclaved diet eighth day
	3.0	0.01	0.08	0.1 mg. of histamine hydrochlorid; autoclaved diet eighth day
9/20/24	5.5	0.03	0.20	0.15 mg. of histamine hydrochlorid; autoclaved diet twenty-second day
	3.5	0	0.08	0.1 mg. of histamine hydrochlorid; autoclaved diet twenty-second day
9/21/24	4.0	0.13	0.25	0.6 mg. of histamine hydrochlorid; autoclaved diet twenty-third day
9/25/24	....	....	....	Discontinued the experiment

Tables 4 and 5 show that the gastric secreting mechanism becomes more refractory as polyneuritis develops in the dog. Thus it required from one and one-half to three times as great histamin doses to bring about a certain maximum secretion of acidity in the last stages of beriberi as in the normal control period.

Table 6 gives the results of similar experiments following the injection of gastrin. Although there appears to be a slight indication of decreased response to gastrin injection as beriberi develops, nevertheless the proportional change is not as great as after the stimulation by a meal or by histamin.

TABLE 6.—*Effect of Autoclaved Diet on Response to Gastrin Stimulation in Dog*

Date	Volume in C.c. First Hour	Free Acidity, per Cent. Hydrochloric Acid	Total Acidity, per Cent. Hydrochloric Acid	Remarks
Experiment 24				
2/ 4/24	5.3	0.33	0.41	1 c.c. of gastrin; fresh diet
2/11/24	3.8	0.33	0.44	1 c.c. of gastrin; fresh diet
2/13/24	4.3	0.25	0.34	1 c.c. of gastrin; fresh diet
3/ 5/24	1.9	0.27	0.37	1 c.c. of gastrin; autoclaved diet fifth day
3/12/24	2.0	0.15	0.26	1 c.c. of gastrin; autoclaved diet twelfth day
3/29/24	4.7	0.28	0.33	1 c.c. of gastrin; autoclaved diet twenty-ninth day
4/ 2/24	....	....	....	Died of beriberi
Experiment 27				
3/ 5/24	5.2	0.33	0.40	1 c.c. of gastrin; fresh diet
3/12/24	5.5	0.27	0.33	1 c.c. of gastrin; fresh diet
3/29/24	5.4	0.35	0.40	1 c.c. of gastrin; autoclaved diet fifteenth day
4/14/24	6.6	0.37	0.43	1 c.c. of gastrin; autoclaved diet thirty-first day
4/16/24	1.3	0.17	0.25	1 c.c. of gastrin; autoclaved diet thirty-third day; symptoms of beriberi
4/20/24	....	....	....	Died thirty-seventh day

TABLE 7.—*Effect of Addition of Yeast Vitamin to Diet Autoclaved with Alkali on Gastric Secretion of Dog (Experiment 42)*

Date	Volume in C.c. for Four Hours	Average Free Acidity, per Cent. Hydrochloric Acid	Average Total Acidity, per Cent. Hydrochloric Acid	Remarks
7/23/24	4.3	0.05	0.13	Fresh diet; good health
7/25/24	3.5	0.04	0.07	Fresh diet; good health
7/27/24	3.6	0.01	0.04	Fresh diet; good health
8/ 2/24	4.1	0.06	0.11	Autoclaved diet plus vitamin; good health sixth day
8/15/24	4.3	0.12	0.22	Autoclaved diet plus vitamin; good health nineteenth day
8/22/24	3.8	0.07	0.12	Autoclaved diet plus vitamin; good health twenty-sixth day
9/ 1/24	6.7	0.22	0.30	Autoclaved diet plus vitamin; good health thirty-sixth day
9/ 7/24	6.6	0.09	0.15	Autoclaved diet plus vitamin; good health forty-second day
9/21/24	3.6	0.01	0.07	Autoclaved diet plus vitamin; good health fifty-sixth day
9/25/24	....	....	....	Good health; discontinued the experiment

Table 7 shows that the addition of Harris yeast vitamin to an alkali autoclaved diet keeps a dog in good condition for some fifty-six days and that the gastric secretion appears to remain normal. The dog used for this experiment was, however, a rather poor secretor. Nevertheless, the good health of the animal proves that in the alkaline autoclaving process the destructive action does not reside in the racemization of the proteins but in the main in destruction of the vitamin. Table 7 simply shows that Harris yeast vitamin does not contain a "gastric secretin" activity similar to that of histamin or of gastrin.

TABLE 8.—*Effect of Injection of Harris Yeast Vitamin Preparation on Gastric Secretion of Dog*

Experiment	Date	Volume Above Continuous Secretion	Free Acidity, per Cent. Hydrochloric Acid	Total Acidity, per Cent. Hydrochloric Acid	Remarks
27	4/16/24	0	—	—	1 tablet injected; sick with beriberi
24	4/ 2/24	0	—	—	1 tablet injected; sick with beriberi
23	4/ 8/24	0	0	0.06	1 tablet injected; recovered from beriberi
28	4/ 8/24	0.1	0	0.03	1 tablet injected; fresh diet
	4/16/24	0	0	0.03	1 tablet injected; fresh diet

CONCLUSIONS

1. Feeding a beriberi producing diet to a dog gradually decreases the total volume as well as the free and the total acidity of gastric secretion.

2. The gastric secretory mechanism of the beriberi dog is not only less responsive to the partaking of food but it is also appreciably more refractive toward histamin hydrochlorid injection. The gastric response after gastrin injection is modified only slightly if at all.

3. The harmful effect of alkali in the autoclaving process is not due to racemization of the proteins but to destruction of the antineuritic vitamin.

4. The antineuritic vitamin is not a gastric secretagogue.

THE HEALING OF GASTRIC ULCERS *

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In a previous article [1] we reported a series of ulcer cases which under medical treatment showed relief of symptoms. When these cases were checked by repeated roentgen-ray examinations, a number of patients showed a gradual diminution and a final disappearance of the ulcer niche. Since the roentgen-ray reports corresponded so closely with the patients' improved clinical condition, we felt that this was strongly suggestive of the healing of the ulcer. Especially was this true in patients who were under 45 years of age and who had had short periods of active symptoms. In specimens resected at operation we were able to show by both gross and microscopic methods several cases of healing of duodenal ulcer. In six cases in which a subtotal gastrectomy had been performed a few weeks after hemorrhage, a healed duodenal ulcer was found in the specimens removed at operation. We were not fortunate enough to obtain specimens that showed convincingly a similar process of healing in ulcers of the body of the stomach. However, as a result of our observations during the last year, we are now able to state that in certain types of gastric ulcer, a like process of healing also takes place following the institution of medical treatment. The proof of the healing of such ulcers consists in the improvement of clinical symptoms, marked diminution in size of the niche, and the corresponding ocular evidence of healing in the specimen removed at the operating table.

REPORT OF CASES

CASE 1.—A man, aged 39, a painter by occupation, with a previous history of arrested pulmonary tuberculosis, had gastric symptoms which began four years before admission with epigastric pain, cramplike in character, occurring at irregular periods after meals. Roentgenographic examination at this point showed a penetrating ulcer of the lesser curvature. The patient was referred to the hospital for medical treatment.

After six weeks reexamination by the roentgenographic method showed a disappearance of the niche.

After this treatment the patient remained well for approximately two years, when he returned with recurrent symptoms, characterized by cramplike pain, sour eructations and vomiting of food, followed by relief of the pain. Roentgen-ray examination showed a small penetrating ulcer at the reentrant angle of

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1. Crohn, B. B.; Weiskopf, Samuel; and Aschner, P. W.: The Life Cycle of Peptic Ulcer, Arch. Int. Med. **35**:405 (April) 1925.

the stomach. After two weeks of conservative medical treatment in the hospital the gastric symptoms disappeared, and examination a few weeks later showed the disappearance of the niche.

For six months he felt well, but returned at the end of that period, again with recurrent symptoms. Another roentgen-ray examination showed a reappearance of the niche at the same site, just above the reentrant angle. The patient was now determined to undergo a radical surgical treatment for the removal of his recurrent ulcer. As his general condition was not satisfactory we determined to institute a preliminary course of medical treatment hoping to improve his strength and nutrition, and incidentally to utilize the opportunity to observe the effects of conservative therapy on the course of a recurrent ulcer. After three weeks of such treatment, the symptoms were considerably relieved, vomiting was allayed and the general condition of the patient was better.

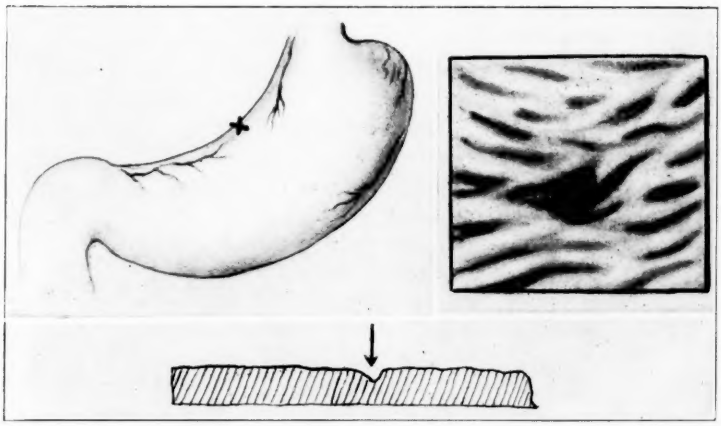

Fig. 1 (Case 1).—Cross section of healing ulcer as removed at operation; shallow depression remaining after healing was almost completed.

A subtotal gastrectomy was then performed by Dr. A. A. Berg; the specimen removed (Fig. 1) showed an ulcer in the advanced stages of healing. A small depression about 3 by 4 mm. in diameter and about 0.5 mm. in depth represented the remains of an ulcer; on palpation there was found to be practically no induration about the lesion. Microscopic section showed the ulcer filled with granulation tissue proceeding from the edges and the base; there was slight edema in the neighborhood of the defect, and some infiltration with round and plasma cells. The sides were contracted until only a small dimple or depression remained as the residuum of the previous ulcer, the defect itself occupying an area corresponding to one microscopic field (low power). The base of the defect was formed by hyaline and somewhat degenerated fibromuscular tissue. Evidently the process of healing, though far advanced, had not yet been carried to the point of epithelialization of complete healing.

Case 2.—A woman, aged 39, fifteen years before admission had suffered with a gastric disturbance for which a cholecystectomy had been performed. An interval of six years followed during which the patient was entirely free from symptoms. At the end of this period epigastric pain recurred about one-half hour after eating. These symptoms lasted from two to three weeks following which another period of freedom of symptoms ensued. During the last eight

years such attacks recurred once or twice a year, each attack lasting from two to four weeks and being followed by a free interval of several months. In the last year her attacks recurred with greater frequency and were longer, thus allowing a shorter interval of freedom of symptoms. In the last two months, during which time she came under the observation of one of us, she had been suffering from continuous symptoms, consisting of postprandial cramplike pain, vomiting and marked loss of weight and strength. Roentgen-ray examination showed a large penetrating niche at the lesser curvature, above the reentrant angle.

In view of the long history with constantly recurring symptoms, particularly the severity of the last attack, it was deemed advisable to urge operation. Here again a preliminary course of medical treatment seemed indicated, the purpose being to improve the general nutrition and strength and to allay the severity of the symptoms, so as to make her a less dangerous surgical risk. After three weeks of such treatment the patient's symptoms were considerably alleviated. At this point a roentgen-ray examination showed an almost complete disap-

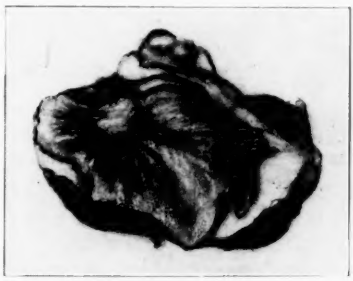

Fig. 2 (Case 2).—Small, shrunken linear scar of penetrating ulcer remaining after course of medical treatment; specimen was excised at operation.

pearance of the previously observed niche. Nevertheless, in view of the past history of repeated severe attacks the original intention of urging operation was adhered to. An excision of the ulcer, with gastro-enterostomy, was performed by Dr. L. M. Kahn at the Lebanon Hospital.

The excised specimen (Fig. 2) showed a linear contracted depression at the site of the previously observed niche, approximately from 6 to 8 mm. in length, about 2 mm. broad, and so superficial in depth that it was almost flush with the surface of the mucous membrane of the stomach, the lateral longitudinal walls being drawn together so as to leave only a linear slit. Microscopic examination of the section through the lesion showed the gastric mucous membrane the seat of a chronic inflammatory lesion with numerous capillaries and round and plasma cells between the glandular acini. One small area of the mucosa presented a mass of granulation tissue (the site of the previous ulcer) the surface of which was partially necrotic (Fig. 3). The central area of the surface was still covered by a thin layer of necrotic membrane. From the sides of the ulcer epithelium with distinct, rather large irregular glandular acini was apparent growing in from both sides.

HISTOLOGIC EVIDENCE OF HEALING

The examination of tissue of these specimens furnished evidence of the method of the reparative process by which at least some ulcers undergo healing under conservative treatment. We find in these ulcer

specimens evidences of healing in successive stages, such as are ably described by Bolton [2] and again more recently in the more exact microscopic studies of Ashkanazy [3] and Perman.[4] The essential process of healing seems to consist of the filling of the crater by the growth of firm granulation tissue from the sides and the base of the ulcer; by the linear retractions of the sides of the ulcer with the approximation of the lateral surfaces (as better demonstrated in our second specimen), and by the ingrowth of newly formed epithelial tissue from the sides of the wound

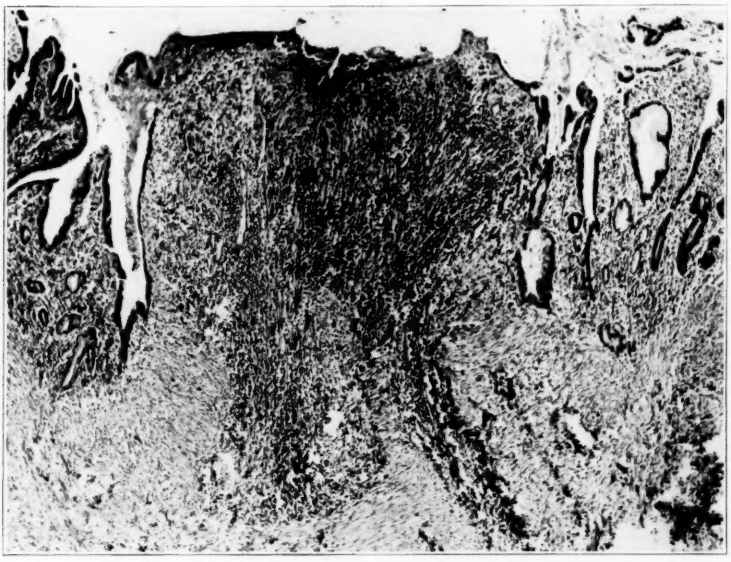

Fig. 3 (Case 2).—Specimen in Figure 2 showing ulcer defect replaced by granulation tissue; new epithelium growing in from both sides and attempting to cover over necrotic membrane that remains on surface of previous ulcer; newly formed blood vessels entering granulation area; muscularis mucosa absent, having been destroyed in ulceration process and not being capable of regeneration.

toward the center. This regenerating epithelial tissue advances from the sides of the healing ulcer as a thin line of columnar epithelial cells showing at the more distal portion, nearer the sides of the ulcer, an increasing tendency to regenerate acini and to form new immature and irregular gastric glands. A definite characteristic in this healing process is the inability to regenerate the portion of muscularis mucosa

2. Bolton: Ulcer of the Stomach, London, 1913.
3. Ashkanazy: Virchows Arch. f. path. Anat. **234**:111, 1921.
4. Perman: Acta Scandinav. Chir. **55**:286, 1923.

destroyed in the course of ulcer. A cross section of such healing ulcer shows the frayed ends of the muscularis mucosa buried in the newly formed granulative tissue.

CORRELATION OF HISTOLOGIC PROCESS OF HEALING WITH CLINICAL AND ROENTGENOGRAPHIC MANIFESTATIONS

In both these cases we have seen that the process of healing marches hand in hand with the regression of the subjective clinical symptoms and the objective evidence of the subsidence of the niche formation in the roentgenogram. It is to be regretted that in the first case cited we failed to obtain a second roentgenographic examination after the institution of a course of medical treatment; this lapse we corrected in our second case by obtaining a roentgen-ray examination immediately before operation and directly after three weeks of medical treatment. The marked diminution in the size of the niche, amounting almost to disappearance, corresponds to the advanced stage of healing evidenced by the specimen in Figure 3.

TYPES OF ULCER IN WHICH HEALING MAY BE ANTICIPATED

We are inclined to accept the classification of gastric ulcers outlined by Sherren.[5] He groups all ulcers as (1) acute, (2) recurrent acute and (3) chronic ulcers. He states quite clearly, as Bolton does also, that acute ulcers most often heal spontaneously on medical treatment. Recurrent acute ulcers, he defines as ulcers in which the onset is sudden, with a short course of clinical symptoms followed by an intermission period of variable length; this cycle tends to recur an indefinite number of times. In the latter type of ulcer, Sherren believes that spontaneous healing in the intermission takes place. In the "chronic" type of ulcer, however, the onset is gradual, symptoms almost continuous, and the chances of spontaneous cure under conservative treatment are rather poor. In a twenty-two year follow-up of a series of cases carried out by Nielsen,[6] he was able to show lasting cure in 60 per cent. of what we would term the acute and the recurrent acute type of ulcer; while in the chronic group of ulcers, healing took place in only 9 per cent. of the cases. These ideas and conclusions bear considerable confirmatory evidence on the observations we have made. We feel that we have added the pathologic evidence necessary to the statement that both acute and recurrent acute ulcers can and do heal in the intermission period. Our clinical observations are substantiated by the roentgen-ray evidence of the disappearance of the niche and both facts are amply strengthened by the gross and histologic demonstrations of the reparative process that takes place in such ulcers during the institution of medical treatment.

5. Sherren: Lancet, March 8, 1924, p. 1477.
6. Nielsen: Acta Med. Scandinav. **58**:286, 1923.

The durability of the healing process is unfortunately problematic. In a fair percentage of cases the healing may be permanent and the clinical symptoms fail to recur. In probably a larger proportion of cases the healing process is incomplete and a tendency to the relapse of the ulcer and of the clinical symptoms is only too often the fact.

UTILIZATION OF PHASE OF HEALING IN INTERPRETATION OF SOME OF MORE OBSCURE TYPES OF GASTRIC CASES

So-called "essential hematemesis" remains one of the questions of medicine today. Clinicians who have thought much on this subject are divided into two schools: (1) those who think that there is always an acute ulcer or erosion (Dieulafoy erosion) as the cause of such bleeding, and (2) those who believe that the gastric mucosa is capable of an essential profuse hemorrhage without a demonstrable organic lesion. (We are excluding from this discussion those cases of gastric hemorrhage in which a hemorrhagic diathesis, purpura, leukemia, Banti's disease or a portal cirrhosis is present to account for the symptoms.)

By observing several of these so-called "essential hematemesis" cases over a course of years, having the advantage of seeing such patients on repeated admissions to the wards or in the outpatient department, certain facts have impressed themselves. We shall not go into a detailed description of the cases which are included in a paper to be published by Stenbuck,[7] in which this subject is fully described and discussed, but we wish to refer to instances in which hematemesis has taken place without previous gastric symptoms. At roentgen-ray examination after the shock of the hemorrhage had passed off, that is, a few weeks later, no organic gastroduodenal lesion could be demonstrated. Cases explored at this moment usually failed to show a lesion. When such cases are followed over a course of years, it has been a not infrequent experience to observe that at some future date the full syndrome of a gastro-intestinal ulceration will occur. If the patient is operated on now, a typical gastric or duodenal ulcer may be found. In this way several cases that we have regarded for years as cases of essential hematemesis have eventually declared themselves as cases of ulcer and a subtotal gastrectomy has placed in our hands a typical ulcer specimen.

One is at a loss to explain why roentgenographic examination and exploratory operation soon after the hemorrhage failed to discover a lesion, for it is on this negative finding that the designation of essential hematemesis has been created. We believe that this explanation lies in the fact that the hematemesis was caused by an acute ulcer, probably not an erosion, but a rapidly forming callous ulcer; that between the time of the hemorrhage and the time of the roentgen-ray examination

7. Stenbuck, J.: To be published.

or exploratory laparotomy the ulcer had partially healed over, defying detection. Since last year we were able to demonstrate six cases of duodenal ulcer that had healed within a few weeks of hemorrhage; we would suggest this explanation as a possible hypothesis to explain the nature of at least some of the cases of "essential hematemesis." With the later recurrence of symptoms the opportunity was placed within our grasp of defining the true nature of the malady as that of peptic ulcer.

Similarly we are often placed in a difficult position to explain the negative findings at an exploratory laparotomy, in cases in which a clear-cut and suggestive history exists, if not a positive roentgenographic examination. It has been our good fortune on several occasions to follow the course of such cases over a period of years and to discover that after a latent period the patient returns with symptoms quite typical of ulcer and a positive roentgenographic examination. An operation performed now yields a positive finding, usually a typically indurated duodenal ulcer.

This experience has repeated itself so often that we feel that the lack of positive findings at the first operation should not merely be ascribed to the shortcomings of the surgeon in palpating the stomach and duodenum in the opened abdomen or to the technical difficulties of demonstrating a small ulceration at such a time. Of late surgeons have not hesitated to incise the stomach or duodenum and carefully to examine the mucosa in an effort to find an ulceration that defies palpation. In this class of case, we feel that the first exploratory operation is performed in a phase of the disease in which the ulcer has undergone regression and temporary healing, while the second exploratory operation is done at a more fortuitous time and discovers the real nature of the disease to be that of ulceration.

We offer this as a hypothesis as to the nature of some of the negative exploratory operations, and feel that the subsequent discovery of an ulcer is to be explained on the basis that these are all variations in the course of the life cycle of ulcer.

SUMMARY

1. In two cases in which partial gastrectomy was performed for gastric ulcer, operation was timed to take place at the end of a course of preliminary medical treatment. The specimens removed showed these ulcers in the last stage of healing. In one case, roentgen-ray examination just before operation showed the disappearance of the niche that had been present.

2. So-called "essential gastric hemorrhage" cases, if operated on soon after the hemorrhage, may show negative findings; if followed over a course of years they may eventually be demonstrated to be true ulcer

cases. It is suggested that the negative findings at the first operation are due to the rapid healing of the ulcer after hemorrhage.

3. The rapid regression of ulcers in the intermission period will explain many of our cases of negative finding at exploratory laparotomy in cases with a suggestive ulcer history. In a series of such cases in which operation was done at a later date during a recurrence of the symptoms, the patient showed definite ulcer.

4. The failure to demonstrate the lesion of a gastric or duodenal ulcer at exploratory laparotomy may therefore be due, at times, to the fact that the operation is carried out at a period in the life cycle of an acute ulcer when rapid regression and healing have obliterated the ulcer crater and made the lesion impossible of discernment.

ACUTE MERCURIC CHLORID POISONING*

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The usual sequence of events following ingestion of lethal doses of mercuric chlorid has become all too familiar in the last ten years. Initially there are abdominal cramps and distress, often with bloody vomitus; diarrhea and melena may follow, and an acute tubular nephritis often supervenes with rapidly developing anuria and death in uremia in from three to twenty days. It has occasionally been noted that the course may be more rapid. Kaufmann [1] cites a case of death with subnormal temperature on the second day. Zangger [2] mentions the possibility of early death as do Oliver,[3] Starkenstein [4] and Cushny,[5] and Burmeister and McNally [6] have evidently observed such cases though they give no details of them. Fussell [7] saw death within twelve hours; Weiss [8] observed death nineteen hours after poisoning and Vaughan [9] states that death may take place in thirty minutes. His description of acute collapse terminating fatally in from twelve to fourteen hours as the common clinical picture is contradicted by the majority of recent observers: Lambert and Patterson,[10] Gatewood and Byfield,[11] Foster,[12] Achard,[13] as

* From the medical clinics of the Johns Hopkins and the Peter Bent Brigham Hospitals.

1. Kaufmann, Eduard: Neuer Beitrag zur Sublimatintoxication nebst Bemerkung über die Sublimatniere, Virchows Arch. f. path. Anat. **117**:227 (Aug.) 1889.

2. Zangger, H.: Die anorganischen Gifte, in Mohr, L., and Staehelen, R.: Handbuch der Innere Medizin, Berlin, 1919, **6**:588.

3. Oliver, Thomas: Metallic and Some Other Forms of Poisoning, in Albutt, Clifford; and Rolleston, H. D.: A System of Medicine, London, 1912, **2**:1007.

4. Starkenstein, Emil: Die anorganischen Gifte, in Kraus, F., and Brugsch, T.: Spezielle Pathologie u. Therapie innerer Krankheiten, Berlin, 1913, **9**:1014.

5. Cushny, A. R.: A Textbook of Pharmacology and Therapeutics, Ed. 7, Philadelphia, 1918, p. 625.

6. Burmeister, W. H., and McNally, W. D.: Acute Mercury Poisoning, J. M. Res. **31**:85 (March) 1917.

7. Fussell, M. H.: In Lambert, S. W., and Patterson, H. S.: Poisoning by Bichlorid of Mercury and Its Treatment, Tr. A. Am. Phys. **30**:282, 1915.

8. Weiss, H. B.: Mercuric Chlorid Poisoning, Arch. Int. Med. **33**:224 (Feb.) 1924.

9. Vaughan, V. C.: Toxicology, in Forchheimer: Therapeusis of Internal Diseases, Ed. 2, New York, 1916, **1.**

10. Lambert, S. W., and Patterson, H. S.: Poisoning by Mercuric Chlorid and Its Treatment, Arch. Int. Med. **16**:865 (Nov.) 1915.

11. Gatewood, L. C., and Byfield, A. F.: A Clinical Report on Acute Cases of Mercuric Chlorid Poisoning, Arch. Int. Med. **32**:456 (Sept.) 1923.

12. Foster, N. B.: Mercury Nephritis, Arch. Int. Med. **15**:754 (May) 1915.

13. Achard, C.: Empoisonnement par le Sublime, Paris méd. **45**:33 (July) 1922. Achard, C., and Rouillard, J.: Forme Benigne de l'Intoxication par le Sublime, La Médecine **4**:444 (March) 1923.

well as by the data of Franz,[14] in whose series of 101 compiled cases with fifty-eight fatalities only one occurred early, although the doses taken were in several cases enormous (from 5 to 10 gm.).

During the years 1923 and 1924, in a series of cases of mercuric chlorid poisoning treated in the medical clinic of Johns Hopkins Hospital, the possibility of early death was brought forcibly to mind. Two of the cases will be given in detail.

REPORT OF CASES

CASE 1.—*History.*—M. W., a white married woman, aged 20, a factory worker, was admitted through the accident room at 9:30 p. m., May 18, 1924, complaining of having swallowed mercuric chlorid. In the history, there were suggestive psychotic data concerning a sister. Her general health had been good. There was an indefinite story of occasional edema of the ankles and periorbital regions for two years, and she had had nocturia for three years intermittently. She had had sore throat frequently but no recognized nephritis. For one and one-half years she had had leukorrhea. She had been married three years; there were two healthy children and no miscarriages recorded.

At 8 p. m., May 18, 1924, she swallowed two 7½ grain (0.49 gm.) tablets of mercuric chlorid. Whether or not she had had supper could not be ascertained. Almost immediately she vomited a brownish fluid; fifteen minutes later she was given two glasses of milk and promptly vomited them, with no accompanying blood. At 9:15 p. m. she was brought to the hospital. In the accident room she was given copious gastric lavage with milk and eggs, and 40 gm. of sodium thiosulphate was introduced into the stomach by tube. Some of this was vomited but the larger part was retained.

Physical Examination.—At 9:30 p. m. on admission to the ward, she was moderately shocked, but the examination was otherwise negative save for marked pyorrhea alveolaris, a heart at the upper limits of normal size, a tender mass in the right pelvis and a suggestion of pretibial edema. The blood pressure was 118 systolic, 84 diastolic.

Blood examination, the following morning revealed: hemoglobin (Sahli), 90 per cent.; red blood cells, 4,860,000; white blood cells, 34,680; a smear not unusual except for 90 per cent. of polymorphonuclear neutrophils in the differential count. Blood drawn immediately after death at 12:40 a. m., May 20, by cardiac puncture, showed nonprotein nitrogen, 98.1 mg., creatinin, 2.97 mg., and chlorids, 420 mg. The blood Wassermann reaction was negative. Urine voided the morning of May 19 was turbid, of 1.020 specific gravity, acid, contained a heavy cloud of albumin (++), no sugar, numerous red and white blood cells and hyaline and cellular casts. The stools were bloody and mucopurulent.

Treatment and Course.—Soon after the patient reached the ward, 1.5 gm. of sodium thiosulphate was given intravenously, and the drug was further given intravenously in 1 and 1.5 gm. dosage at 8 a. m. and 6 p. m., May 19. A solution of 0.8 per cent. each of potassium acetate and sodium thiosulphate was given continuously by rectal drip method, and 200 c.c. of milk with 4 gm. of sodium thiosulphate or an equal amount of potus imperialis was given by mouth at alternate hours. The afternoon of May 19, 5,000 c.c. of physiologic sodium chlorid solution was given by subpectoral infusion. High colonic irrigations with 0.4 per cent. of sodium thiosulphate solution were undertaken and potassium chlorate mouth wash was used frequently. A total of 40 gm.

14. Franz, F.: Die im Deutschen Reich wahrend der Jahre 1897-1905 amtlich gemeldeten Vergiftungen mit Sublimat, Arb. a. d. k. Gsndhsamte **34**:1 (March) 1910.

of sodium thiosulphate was given by mouth after the patient reached the ward. During the first night in the ward, the patient vomited frequently and was incontinent of urine. The passage of urine was not observed after 10 a. m., May 19. The vomiting had ceased; she was less shocked and took fluids well by mouth, but she was rather dulled mentally in the afternoon and in the evening developed active delirium and pulled out the subpectoral needle. At 11 p. m. she suddenly became cyanosed; her breathing was slow and shallow and her extremities were cold. In spite of caffein sodium benzoate and strophanthin subcutaneously and intramuscularly, she became comatose; her pulse weakened; she developed Cheyne-Stokes breathing and the heart stopped at 12:40 a. m., May 20. Intracardiac epinephrin had no effect. Necropsy was refused.

CASE 2.—*History.*—M. J. J., a white married woman, aged 35, was admitted through the accident room, May 20, 1924, at 12:30 p. m., complaining of having swallowed mercuric chlorid. For several years she had had occasional swelling of the ankles and transient edema beneath the eyes; for a similar period she had had occasional nocturia. The tubes and ovaries were said to have been removed two years before. Otherwise, the history was negative. Of three pregnancies, one was a miscarriage; two children were living and well.

At 8 a. m. the morning of admission, she had eaten an egg, bacon, bread and coffee. At 10:30 a. m. she swallowed four 7½ grain (0.49 gm.) tablets of mercuric chlorid. Almost immediately she was given milk by mouth, and vomiting ensued; the vomitus was bluish but contained no particles of tablets. At 12:15 p. m. she came to the accident room where copious gastric lavage was instituted and 3 gm. of sodium thiosulphate was left in the stomach.

Physical Examination.—At 12:30 p. m., on admission to the ward, she was somewhat dazed and complained of pain in the throat and stomach. She was vomiting small quantities of fluid with which were mixed shreds of mucus, bits of tissue that were apparently gastric mucosa, and small quantities of blood. She presented exceptionally short arms and legs in relation to trunk length without actually appearing achondroplastic. The examination revealed tenderness in the episternal notch, diffuse abdominal tenderness without spasm and a suggestion of edema of the ankles. Blood examination, at about 2 p. m., revealed: hemoglobin (Sahli), 65 per cent.; red blood cells, 4,120,000; white blood cells, 40,000; a smear not unusual except for 92 per cent. of polymorphonuclear neutrophils in the differential leukocyte count. The blood Wassermann reaction was negative. Blood drawn by cardiac puncture immediately after death showed nonprotein nitrogen, 23.3 mg., creatinin, 2 mg., and chlorids, 478 mg. Urine voided soon after reaching the ward was of 1.008 specific gravity, reaction not recorded; albumin + +, no sugar; there were many white blood cells and cellular casts in the sediment but no red blood cells and it gave a negative guaiac test.

Treatment and Course.—Within five minutes after the patient reached the ward, she was given 1.5 gm. of sodium thiosulphate intravenously in 50 c.c. of fluid. Because of the character of the vomitus and the abdominal tenderness, it was considered unwise to force fluids by mouth and provoke further vomiting; a solution of 0.8 per cent. each of sodium thiosulphate and potassium acetate was given by rectal drip method, and of this about 600 c.c. was absorbed. In the early afternoon, 1,100 c.c. of physiologic sodium chlorid solution was given as a subpectoral infusion. At 4 p. m. she was given 200 c.c. of potus imperialis, which she retained, as she did an equal volume of milk with 2 gm. of sodium thiosulphate given thirty minutes later. She voided on reaching the ward, but not afterward. At 3 p. m. she was mildly delirious. At 4 p. m. before she began fluids by mouth, the abdomen was examined and found soft and not tender. At 5 p. m., as preparations were being made for a second intravenous injection of sodium thiosulphate, she suddenly collapsed, with cyanosis, shallow breathing,

a slow but thready pulse, profuse sweating and total unresponsiveness; she died within five minutes. Intracardiac epinephrin had no effect.

At necropsy at 9 p. m., May 20, for the record of which I am indebted to Dr. S. M. Seidlin of the Department of Pathology of Johns Hopkins University, the positive gross findings were as follows: The mucosa of the esophagus was slightly congested. The stomach contained 200 c.c. of yellowish, semifluid, coagulated material; the wall was everywhere congested, and there were two areas of necrosis 7 by 4 and 2 by 3 cm. in diameter in the wall, without perforation. The duodenal mucosa was slightly hyperemic, as was that of the cecum. The kidneys weighed 150 and 160 gm.; their capsules stripped readily; the surface was smooth and pink. The cortical portion did not appear enlarged or swollen but, in places, rather opaque. The striae were in many places very indistinct, but there were no hemorrhages. There was a cyst in the right broad ligament. The heart, lungs, spleen, liver, suprarenals and marrow appeared normal.

Microscopically, the kidneys showed extensive necrosis of the tubular epithelium with desquamation; this destroyed almost all the convoluted tubules. There was no calcification. The collecting tubules were well preserved, but some were filled with casts. The glomeruli, the capsules, the vessels and the mucosa of the pelves and calices were normal. Dr. Seidlin's impression was that the kidneys had received recent injury but that there was no evidence of active inflammatory change. Sections of the injured stomach wall showed necrosis, edema, congestion of vessels and hemorrhages. The uterine endometrium had the hyperplastic appearance usually seen before menstruation. The broad ligament cyst showed normal ovarian tissue. The heart, liver, spleen, suprarenals, pancreas, thyroid and bone marrow were normal, and the lungs showed edema and thickening of the alveolar walls in some places, and one or two nodules probably representing an old tuberculosis.

The cause of death shortly after mercurial poisoning has been studied in animals without definite conclusions. Von Mering,[15] using subcutaneous dosage, observed sudden collapse and death in an agonal state in several instances. The accompanying fall in blood pressure he showed was not relieved by sectioning the vagi. MacNider[16] found that of a group of dogs who received the drug by stomach, a certain number promptly developed an intense gastro-enteritis and died in collapse and shock with subnormal temperature, cyanosis, shallow breathing, rapid heart action and feeble heart sounds. Salant[17] observed a fall in blood pressure soon after introduction of mercuric chlorid into the duodenum, followed by evidence of cardiac damage, arrhythmia, including complete heart block, and circulatory collapse. Lee[18] considers the drug a definite cardiac depressant, and thinks this action probably responsible for early deaths, of which he gives no instances. Cushny,[5] on the contrary, suggests that the fall in blood pressure is probably the result of peripheral

15 Von Mering, J.: Ueber die Wirkungen des Quecksilbers auf den thierischen Organismus, Arch. f. exper. Path. u. Pharmakol. **13**:86 (Oct.) 1880.

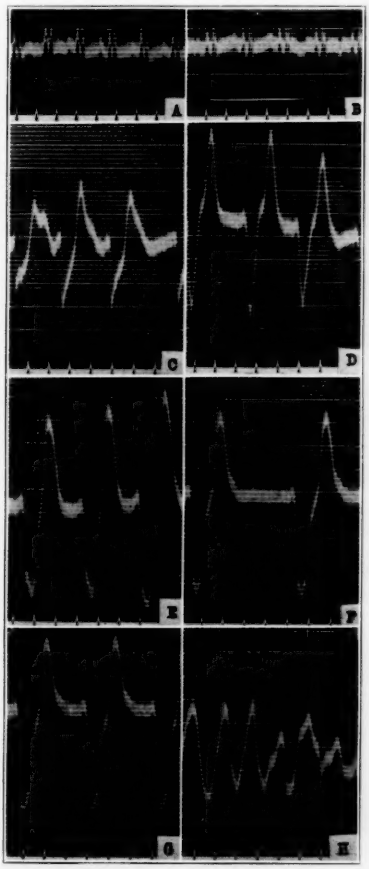
16. MacNider, W. D.: A Study of Acute Mercurial Chlorid Intoxication in the Dog with Special Reference to the Kidney Injury, J. Exper. Med. **27**:519 (April) 1918.

17. Salant, William: Pharmacology of Mercury, J. A. M. A. **79**:2071 (Dec. 16) 1922.

18. Lee, R. V.: The Pharmacology of Mercury, J. A. M. A. **81**:1748 (Nov. 24) 1923.

small vessel paralysis, together with dilatation of the splanchnic circulation incident to local action of the drug on the gastro-intestinal tract.

At the suggestion, and with the aid, of Dr. S. A. Levine, an attempt was made to observe direct action of the drug on the myocardium, using the intravenous method in a cat and the string galvanometer as employed



Lead II in etherized cat weighing 2.7 kg.; *A*, control lead; *B*, six minutes after 10 mg. of mercuric chlorid intravenously; *C*, four minutes later, total dosage 20 mg., blood pressure falling; *D*, six minutes later, total dosage 30 mg., pressure still falling; *E*, six minutes later, total dosage 35 mg.; *F*, four minutes later, total dosage 45 mg., pulse barely perceptible; *G*, two minutes later, total dosage 45 mg., respirations failing, and *H*, three minutes later, total dosage 55 mg., animal apparently dead.

by Levine [19] in studying the effects of digitalis bodies. Under light ether anesthesia, the femoral artery and vein were exposed and cannulated; 100 mg. of heparin was injected intravenously to avoid coagulation; the arterial cannula was connected with a sensitive manometer and a glass buret containing mercuric chlorid in dilute solution in physiologic sodium chlorid solution was attached to the venous side. The customary galvanometric leads were established and, after a preliminary electrocardiogram, mercuric chlorid solution was run in intermittently, frequent tracings of the blood pressure and heart action currents being taken.

As may be seen in the accompanying figure, the smallest dose employed reduced the voltage, and slightly larger doses gave evidence of severe myocardial damage as shown by the abnormal ventricular complexes recorded, as well as by a coincident fall in peripheral blood pressure. Successive doses increased this effect; the blood pressure fell progressively, and the evidence of heart muscle damage proceeded. *F* and *G* are apparently the tracings of a dying heart, and death occurred with ventricular fibrillation. With slight variations, this evidence of toxic action of relatively small doses was present in other experiments. There is nothing specific about the later changes in the electrocardiograph; Gordon [20] obtains similar records in cats receiving quinidin intravenously, but they are not merely the accompaniment of death in the cat, as they do not appear when animals are bled to death. It was not intended to determine the toxic dose of mercuric chlorid by this method but to ascertain whether evidence of direct action on the heart, from small quantities of drug, which might play a part in the intoxication, could be obtained. The quantities of mercuric chlorid per kilogram which showed this action were of the same order as might be assumed for absorbed mercuric chlorid from the average amount ingested by human beings.

Failure to demonstrate morbid changes at necropsy other than those of local escharotic action is not surprising. The degree of nephritis found in the second patient was considered fairly early for mercuric chlorid nephritis in man, but Fiessinger [21] examined the kidneys of guinea-pigs at intervals after intraperitoneal injection of from 0.008 to 0.017 gm. of sublimate in solution, amounts that are of the same general magnitude per kilogram as the usual human dosage by mouth, and he described a patchy and irregular involvement of a few tubules after one hour of poisoning, in which the only lesions found were swelling of the cytoplasmic granules and slight pyknosis of the nuclei without exudate

19. Levine, S. A.: The Action of Strophanthin on the Living Cat's Heart, J. Exper. Med. **29**:485 (May) 1919.

20. Gordon, Burgess: Personal communication to the author.

21. Fiessinger, Noel: Note sur les Lesions Renales, au cours de l'Intoxication Mercurielle Massive, Compt. rend. Soc. de biol., Feb. 16, 1907, p. 240.

or desquamation into the lumen. The changes found in this patient, however, could have had little to do with death. The rapidity with which nitrogen retention can develop is emphasized by Case 1, in which, with anuria of less than fifteen hours, the level of nonprotein nitrogen reached 98 mg.

Of great interest were the high leukocyte counts (34,000 and 40,000) recorded in these fatal cases. In a number of other cases similarly high counts were observed only once. This was in a man, aged 25, whose blood showed 40,500 white cells per cubic millimeter eight hours after taking an unknown amount of mercuric chlorid, and who died fifty hours after the poisoning with a terminal Type IV pneumococcus pneumonia, showing at necropsy inflammation of most of the gastro-intestinal tract from mouth to colon, extreme necrosis of the renal tubules, pneumonia and fibrinous pleurisy. It is interesting that in this case, in spite of the development of secondary infection, after forty-eight hours the leukocytes numbered only 9,800. Heilborn [22] found deep red marrow in the hollow bones of rabbits and the femurs of dogs experimentally mercurialized. Kaufmann [23] noted an increase in white blood cells and rapidly developing anemia in experimental poisoning. Clinically, Guillain and Gardin [24] saw a white count of 13,400 and anemia of 3,300,000 red cells on the third day in a case terminating in uremia on the eighteenth day. Vialard and Baril [25] counted 21,700 white cells with 89 per cent. polymorphonuclear neutrophils on the thirteenth day after mercuric cyanid poisoning, and Outerbridge [26] found 14,400 leukocytes on the second day in a patient who recovered from vaginal absorption of mercuric chlorid after a stormy course. Weiss [8] alone has apparently attached significance to this leukocytosis, which, he says, may reach 20,000 and then decline, or remain elevated and carry an unfavorable prognosis. Persistent elevation of the count we have not observed, but it would seem that early in the disease it is of definite importance as an index of the likelihood of recovery, as in ten other cases the degree of elevation of the white count corresponded closely with the severity of the poisoning; the patients with normal counts escaped colitis and

22. Heilborn, Max: Experimentelle Beitrage zur Wirkung subcutaner Sublimat-Injectionen, Arch. exper. u. Pharmakol. **8**:361 (Jan.) 1878.

23. Kaufmann, Eduard: Die Sublimatintoxication, Thesis, Breslau, 1888, cited by Besseson, D. H.: Arch. Dermat. & Syph. **7**:332 (March) 1923.

24. Guillain, G., and Gardin, C.: Physiologie Pathologique de l'Intoxication Mortelle par le Sublime, Ann. de méd. **11**:338 (April) 1922.

25. Vialard and Baril: Etude sur deux cas d'Intoxication, dont l'un mortel, par absorption d'un sel de mercure, Bull. et mém. Soc. méd. d. hôp. de Paris **47**: 907 (June) 1923.

26. Outerbridge, G. W.: Complete Anuria Following a Mercuric Chlorid Douche; Recovery After Bilateral Renal Decapsulation, J. A. M. A. **80**:102 (Jan. 13) 1923.

nephritis, and several with a moderate increase (up to 20,000) exhibited definite but mild signs and symptoms of one or the other.

Last, the recent revival of interest in chemical detoxication, stimulated by the work of McBride and Dennie,[27] leads to a word of warning. Early and intensive treatment with sodium thiosulphate may not prevent early toxic death, and the generally accepted scheme of therapy (for example, that of Lambert and Patterson [10]), forced fluids, alkali or its equivalent in alkaline tartrates and citrates, gastric lavage and colonic irrigations, should by no means be neglected. Attempts to prove experimentally the value of other antidotes [28] that seemed efficacious clinically have been fruitless, and Zeigler's comment that recovery apparently takes place independently of the administration or failure to administer any of these so-called specific chemical detoxicants seems well taken. Variations in the lethal dose by mouth are so extreme that a large number of clinical observations, with an equal number of controls, should precede conclusion as to the value of any single therapeutic measure in this disease.

SUMMARY

Death from mercuric chlorid taken by mouth may ensue within hours, apparently with circulatory collapse, with little renal damage and no evidence of uremia. Evidence is presented which suggests that direct myocardial damage may account in part, at least, for this early toxic death. In three severely poisoned cases, the white count reached 34,000 or higher in a few hours, and it is suggested that the degree of elevation of the leukocytes may be an index of the severity of poisoning, with an unfavorable prognosis when levels of from 30,000 to 40,000 are found. Last, while it is not denied that sodium thiosulphate may have value in treatment, it should be emphasized that it may fail to exert detoxicant action, and should not be administered to the neglect of established therapeutic methods.

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27. McBride, W. L., and Dennie, C. C.: Treatment of Arsphenamin Dermatitis and Certain Other Metallic Poisonings, Arch. Dermat. & Syph. **7**:63 (Jan.) 1923; Treatment of Arsphenamin Dermatitis, Mercurial Poisoning and Lead Intoxication: Further Observations, J. A. M. A. **83**:2082 (Dec. 27) 1924.

28. Barbour, H. G.: Mercuric Chlorid Poisoning in Animals Treated Unsuccessfully by Parenteral Administration of Hall's New Antidote, J. A. M. A. **64**: 736 (Feb. 27) 1915. Zeigler, W. H.: A Study of the Efficiency of Certain Antidotes in the Treatment of Acute Bichlorid of Mercury Poisoning, J. Lab. & Clin. Med. **10**:59 (Jan.) 1925.

THE INORGANIC PHOSPHORUS AND CALCIUM OF THE BLOOD IN NEPHRITIS *

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It has been recognized for several years that the terminal stages of nephritis are accompanied by an increase in the inorganic phosphorus of the blood serum and some decrease in the calcium.

In 1915 Greenwald [1] reported observations on the acid-soluble (largely inorganic) and lipoid phosphorus of human blood serum. He observed that normally the acid-soluble phosphorus as P varied between 2 and 6 mg. per hundred cubic centimeters, but that in severe nephritis it might be considerably increased. A year later Marriott and Howland [2] confirmed these observations and pointed out that the retention of (acid) phosphate would seem to be sufficient to account for the degree of acidosis observed. They found further in most of their cases a marked reduction in the calcium of the serum. They state:

> What influence this low calcium content may have on the production of such symptoms as convulsions and hemorrhages can only be suggested. The low calcium content is referred to the excess of phosphates in the plasma. It has repeatedly been shown that phosphates administered in any form cause an increased elimination of calcium, chiefly by way of the intestine.

In 1917 Halverson, Mohler and Bergeim [3] studied the serum calcium of several patients with severe nephritis and obtained figures as low as 7 mg. Denis and Minot [4] in 1920 reported observations on the inorganic phosphorus of a comparatively large series of nephritic patients (eighty). They observed that the fatal cases showed a rapid and progressive increase in the plasma phosphate, figures more than ten times

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† Medical fellow of the National Research Council during part of this study.

1. Greenwald, I.: The Estimation of Lipoid and Acid-Soluble Phosphorus in Small Amounts of Serum, J. Biol. Chem. **21**:29, 1915.

2. Marriott, W. M., and Howland, J.: Phosphate Retention as a Factor in the Production of Acidosis in Nephritis, Arch. Int. Med. **18**:708 (Nov.) 1916.

3. Halverson, J. O.; Mohler, H. K., and Bergeim, O.: The Calcium Content of the Serum in Certain Pathological Conditions, J. Biol. Chem. **32**:171 (Nov.) 1917.

4. Denis, W., and Minot, A. S.: A Study of Phosphate Retention from the Standpoint of Blood Analysis, Arch. Int. Med. **26**:99 (July) 1920.

the maximal normal value being noted (over 40 mg. in one case); the nonfatal cases, even though the patients were seriously ill, presented a relatively slight increase. As a result of these findings they suggested that the determination might possess considerable prognostic value. They found no concordance between the increased content of inorganic phosphate and the nonprotein nitrogen in confirmation of the findings of Greenwald, and Marriott and Howland. They also called attention to the lack of any definite relation between the plasma phosphate and the alkaline reserve, a finding of interest in connection with the suggested relation between the acidosis in nephritis and phosphate retention. More recently Denis and Hobson [5] have determined the various inorganic constituents of the serum, both acids and bases, in a series of twenty nephritis cases. The series did not include the severe cases of the earlier paper, the inorganic phosphorus being as high as 10 mg. in only one case. The lowest calcium observed was 7.6 mg. Feigl [6] has likewise presented figures for the acid-soluble phosphorus, also the calcium, in a series of eight severe nephritic cases, the phosphorus varying between 7.2 and 14.5 mg. per hundred cubic centimeters of serum and the calcium between 7.4 and 10.3 mg. Salvesen and Linder [7] have recently studied the inorganic bases and phosphates in relation to the proteins of the blood in a series of fifteen cases of Bright's disease and heart disease. Their series included two cases of uremia, six cases of chronic glomerulonephritis and three cases of nephrosis. The two uremia cases showed calcium figures of 6.8 and 7.2 mg. and inorganic phosphorus figures of 20.5 and 24.0 mg., respectively. They pointed out that the decrease in serum calcium in nonuremic cases of Bright's disease without phosphate retention paralleled the decrease in plasma protein. This they believed was due to a decrease in the nondiffusible portion of the calcium (20-45 per cent.) which is bound to the plasma proteins. However, in the cases with phosphate retention they regard this as the probable cause of the reduction in the calcium, since Binger [8] has shown that the injection of phosphates results in a lowering of the blood calcium.

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5. Denis, W., and Hobson, S.: A Study of the Inorganic Constituents of the Blood Serum in Nephritis, J. Biol. Chem. **55**:183 (Feb.) 1923.

6. Feigl, J.: Neue Beiträge zur Kenntnis der anorganischen Stoffe des Blutes, I, Kationen und Hyperphosphatämie bei Morbus Brightii, Ztschr. f. physiol. Chem. **3**:280, 1920.

7. Salvesen, H. A., and Linder, G. C.: Observations on the Inorganic Bases and Phosphates in Relation to the Protein of the Blood and Other Body Fluids in Bright's Disease and Heart Failure, J. Biol. Chem. **58**:617 (Dec.) 1923.

8. Binger, C.: Toxicity of Phosphates in Relation to Blood Phosphates and Tetany, J. Pharm. & Exper. Therap. **10**:105 (Aug.) 1917.

In two comparatively recent papers, de Wesselow [9] has focused attention on the relation of the content of calcium, inorganic phosphorus and urea of the blood to the clinical symptoms and prognosis of nephritis, particularly when associated with uremia. He has presented some interesting data and raises a number of points, some of which will be discussed further in connection with our own data.

De Wesselow is of the opinion that although nitrogen retention is a valuable prognostic index of the severity of nephritis, nitrogen retention per se is harmless. He points out that on the average the retention of phosphates and urea runs a parallel course, and concludes that the excretory mechanism of the two bodies is therefore probably the same. He regards a marked increase of the inorganic blood phosphorus in nephritis as an extremely grave prognostic sign, and notes that the symptoms of uremia appear to show a close relationship to phosphate retention. The calcium content of the serum seemed to show an inverse relationship to the content of inorganic phosphorus. According to de Wesselow a diminished content of serum calcium is a bad omen, and appears to be connected with the generalized tremor and local twitchings of the final stages of uremia, but not to the generalized convulsions. Of ten fatal cases, in which the calcium was estimated, the serum contained less than 7 mg. per hundred cubic centimeters in nine cases, the lowest observation being 5.1 mg.

OBJECTS OF PRESENT STUDY

Our interest in this general problem was aroused by the paper of Marriott and Howland in 1916 and we had compiled a considerable number of observations on the serum calcium prior to the present study, although the data [10] were never reported in detail.

The present study was undertaken with the hope of securing added information on the following points: (1) the possible relation of a reduction in the serum calcium to the convulsions and muscular twitchings of terminal chronic interstitial nephritis; (2) the relation of the retention of inorganic phosphorus to the reduction in the serum calcium; (3) the relation of the rise in the inorganic phosphorus of the blood to the lowering of the plasma bicarbonate, and (4) a comparison of the rise of the inorganic phosphorus and creatinin as prognostic signs.

Observations were made on fifty-four patients, the majority of whom were suffering from chronic interstitial nephritis. The data are pre-

9. De Wesselow, O. L. V.: On the Phosphorus and Calcium of the Blood in Renal Disease, Quart. J. Med. **16**:341 (July) 1923; The Immediate Prognosis in Nephritis, with Some Remarks on Uremia, Lancet **2**:163 (July 28) 1923.

10. Myers, V. C., and Killian, J. A.: Chemical Changes in the Blood in Advanced Nephritis, Proc. Soc. Biol. Chem., April, 1919; J. Biol. Chem. **41**:21, 1920.

TABLE 1.—*The Inorganic Phosphorus and Calcium of the Blood in Nephritis*

Case	Age	Sex*	Date	Inorganic Phosphorus, Mg. to 100 C.c.	Calcium, Mg. to 100 C.c.	Urea Nitrogen, Mg. to 100 C.c.	Creatinin, Mg. to 100 C.c.	Uric Acid, Mg. to 100 C.c.	Carbon Dioxid, per Cent. by Volume	p_H	Diagnosis and Remarks
1	26	♂	1/23/24	25.5	6.8	125	7.5	...	44	....	Chronic nephritis; convulsions; received alkali; died 1/25
2	26	♂	8/ 8/22	20.2	9.5	98	19.6	6.3	20	....	Chronic nephritis; died
3	65	♂	5/ 5/24	....	...	167	18.7	...	31	....	Chronic nephritis; diabetes; muscular twitchings 5/9; died 5/13
			5/ 8/24	18.2	6.9	165	....	...	33		
			5/12/24	11.1	...	142	....	...	36		
4	34	♂	5/28/24	17.4	...	147	27.4	...	..	....	Chronic nephritis; died 5/30
5	31	♂	9/ 5/23	12.6	5.6	197	22.7	9.3	20	....	Chronic nephritis; convulsions for ten minutes 9/9; died 9/17
			9/10/23	15.6	4.3	106	25.0	...	37	7.37	
			9/15/23	16.4	3.8	...	....	...	56	7.35	
			9/17/23	17.2							
6	8	♂	5/ 8/23	12.1	4.8	89	....	...	25	7.15	Nephrosis followed two years later by chronic nephritis; transfusion 5/25; convulsions 6/3, day of death
			5/11/23	....	...	98	11.1	6.8	30		
			5/14/23	15.1	4.4						
			5/18/23	15.0	4.2	...	....	...	19	7.29	
			5/25/23	12.0	4.1	86	11.5	5.0	20	7.22	
			5/28/23	15.2	...	109	12.4	4.6	21	7.16	
			5/30/23	15.0	...	.	....	...	..	7.18	
			6/ 2/23	16.1	...	...	....	...	..	7.05	
7	54	♂	3/26/24	12.4	7.8	108	21.0	...	27	7.23	Chronic nephritis; uremia; convulsions; died 3/29
			3/28/24	14.4	6.9	139	21.1	7.0			
8	15	♀	12/13/23	12.2	4.8	100	20.0	13.7	24	....	Chronic nephritis; convulsions one week before admission; died (suffered from nephrosis in 1916)
			12/13/23	13.9							
9	46	♂	10/ 4/22	4.4	12.0	66	5.4	...	..	....	Chronic nephritis; no convulsions; died
			10/19/22	6.6	9.4	49	7.5	4.1	31		
			10/23/22	6.6	9.5	86	8.4	6.8	39		
			10/27/23	8.7	9.5	122	11.5	8.4	49		
			10/28/22	10.0							
			10/30/22	12.2	7.1	155	13.4	...	35		
			11/ 1/22	12.2	6.5						
10	22	♂	4/24/23	9.2	5.5	130	20.5	...	29	7.16	Chronic nephritis; convulsions 5/17; died 5/19
			4/30/23	10.8	...	...	....	...	..	7.22	
			5/ 7/23	10.4	...	112	23.0	7.8	43		
			5/14/23	11.9	5.6	122	20.3	7.7	40	7.28	
11	37	♂	6/ 4/23	11.9	...	111	16.2	4.6	20	7.17	Carcinoma of kidney; convulsions 6/9; died
12	39	♀	11/26/23	....	...	56	7.5	...	..	....	Chronic nephritis; no convulsions; died 12/4
			11/28/23	....	...	75	9.3	...	55		
			12/ 3/23	11.8	8.2						
13	30	♀	7/15/23	11.3	...	87	.....	...	..	....	Chronic nephritis; died 7/15
14	50	♂	11/ 1/23	8.7	...	55	4.3	5.0	42	....	Chronic nephritis; died
			11/ 7/23	11.1	...	104	14.4	9.3	24		
15	41	♂	8/ 8/22	9.8	9.5	155	14.0	...	30	....	Chronic nephritis; died
16	46	♀	1/18/23	6.1	...	49	4.9	6.2	61	....	Chronic nephritis; uremia; hypertension; mitral stenosis and insufficiency; convulsions 3/2/23; one lasting 2 minutes, another 8 minutes; died
			1/22/23	6.2	...	72	....	6.9			
			1/26/23	6.4	11.7	...	....	...	73		
			1/30/23	5.7	11.5	68	7.0	6.1	60		
			2/ 5/23	5.8	7.0	40	6.5	5.8	62		
			2/12/23	7.1	...	55	....	...	61		
			2/19/23	4.9	9.0	50	5.6	5.8	54		
			2/26/23	8.6	9.0	60	8.2	8.9	57		
			2/28/23	9.3	...	74	9.6	9.5	55		
17	63	♀	2/ 1/24	11.0	9.6	43	5.4	...	..	....	Chronic nephritis; cardiac disease; bronchopneumonia; 90 gm. sodium bicarbonate given 2/8-9; died 2/10
			2/ 9/24	9.5	9.3	105	15.0	9.0	24	7.22	

* In this table, ♂ indicates male; ♀, female.

TABLE 1.—*The Inorganic Phosphorus and Calcium of the Blood in Nephritis—Continued*

Case	Age	Sex*	Date	Inorganic Phosphorus, Mg. to 100 C.c.	Calcium, Mg. to 100 C.c.	Urea Nitrogen, Mg. to 100 C.c.	Creatinin, Mg. to 100 C.c.	Uric Acid, Mg. to 100 C.c.	Carbon Dioxid, per Cent. by Volume	p_H	Diagnosis and Remarks
18	19	♂	9/11/22	8.8	6.0	158	20.0	13.2	41	....	Chronic nephritis; died 10/10
			10/ 9/22	14.3							
19	38	♀	2/26/23	6.5	10.0	96	3.6	...	52	7.47	Acute nephritis; acute mastoiditis; alkali given; died 3/9
			2/27/23	....	...	115	5.3				
			2/29/23	....	...	127	....	...	58	7.48	
			3/ 4/23	....	...	156	....	...	43		
			3/ 5/23	....	...	163	....	...	56		
			3/ 6/23	8.7	10.0	185	....	...	..	7.48	
			3/ 7/23	....	...	211	....	...	58		
			3/ 8/23	9.2	...	208	11.0	12.0			
20	32	♂	1/22/23	6.0	...	32	4.6	3.9	..	....	Chronic nephritis; died
			1/26/23	8.7	...	57	11.5	4.0	33		
			1/30/23	8.5	...	54	7.8	4.3	38		
21	50	♂	3/ 9/24	8.0	5.4	172	11.5	...	..	....	Chronic nephritis; died 3/10
22	44	♂	7/21/24	7.7	7.9	59	8.6	5.0	42	....	Chronic nephritis; hypertension
23	46	♂	10/22/23	8.2	9.4	103	11.0	...	54	7.40	Chronic nephritis; no convulsions; discharged clinically improved 11/10
			10/30/23	7.5	8.8	109	14.2	...	35		
			11/ 5/23	....	...	100	12.5	...	61	7.40	
24	..	♂	6/ 1/23	7.5	...	82	7.2	4.9			
			6/ 2/23	7.3	...	...	....	...	64		
25	37	♂	12/18/23	7.4	5.7	83	5.2	...	35	....	Chronic nephritis; discharged improved 12/24
26	43	♂	10/ 4/22	4.3	10.5	61	6.2	...	42	....	Cardiorenal disease; no convulsions; died
			11/ 6/22	4.2	11.2	30	3.4	4.7	54		
			11/27/22	5.8	...	46	4.7	5.0	63		
			12/11/22	4.7	...	60	6.3	5.3	51		
			1/ 2/23	4.1	...	48	7.4	5.6	56		
			1/15/23	5.1	...	49	6.0	7.6	61		
			1/22/23	5.1	9.2	63	8.3	7.5			
			1/26/23	4.7	10.8						
			2/16/23	7.0	8.0	74	4.4	5.8	51		
			2/19/23	5.7	8.6	70	4.3	...	52		
			2/25/23	8.7	8.4						
27	36	♂	11/12/23	6.6	9.0	34	4.4	3.8	..	....	Nephrosis; chronic nephritis
28	33	♂	6/20/23	4.8	...	47	3.7	...	..	....	Cardiorenal disease; died 11/1
			6/27/23	5.9	...	70	5.0	4.8	30		
			7/ 4/23	6.3	...	34	....	...	51	7.36	
			7/ 9/23	6.3	...	63					
			7/30/23	5.0	...	24	2.8	3.6			
			9/24/23	4.6	8.6	22	3.4	4.4	44		
29	35	♂	4/17/23	6.1	7.7	60	9.0	5.3	31	....	Chronic nephritis; discharged improved 4/28
			4/27/23	7.0	6.6						
30	26	♂	2/ 4/23	5.2	9.6	44	5.5	...	..	....	Chronic nephritis; severe uremic convulsions; died 2/16
			2/15/23	6.0	10.0	135	11.1	...	65		
31	53	♀	1/19/23	5.2	...	24	3.4	3.5	38	....	Pyonephrosis; hypertension; discharged clinically improved 1/22
			1/22/23	5.9	...	24	4.1	3.6	33		
32	44	♂	8/ 1/23	5.9	...	90	8.4	...	..	....	Chronic nephritis; died
33	65	♂	9/24/23	5.9	8.9	66	7.1	6.6	49	....	Chronic nephritis; left hospital clinically improved 12/24
			10/ 6/23	8.5	7.3	84	9.2				
			12/17/23	5.7	...	42	6.2	...	60		
34	70	♂	10/13/22	5.7	...	63	5.0	4.2	..	....	Chronic nephritis
35	50	♂	3/ 9/23	5.7	7.6	74	7.9	5.7	29	....	Chronic nephritis; left hospital 3/20
			3/12/23	6.3	8.3						
36	50	♂	4/13/23	5.5	11.2	54	4.1	6.3	39	...	Prostatic hypertrophy; operation; discharged improved 5/27
			4/19/23	4.5	10.2	45	4.8	4.8	46	7.33	
			4/24/23	3.4	10.5	16	....	4.0	66	7.35	

* In this table, ♂ indicates male; ♀, female.

TABLE 1.—*The Inorganic Phosphorus and Calcium of the Blood in Nephritis—Continued*

Case	Age	Sex*	Date	Inorganic Phosphorus, Mg. to 100 C.c.	Calcium, Mg. to 100 C.c.	Urea Nitrogen, Mg. to 100 C.c.	Creatinin, Mg. to 100 C.c.	Uric Acid, Mg. to 100 C.c.	Carbon Dioxid, per Cent. by Volume	p_H	Diagnosis and Remarks
37	28	♂	1/17/24	4.7	8.7	13	....	...	..	....	Nephrosis; left hospital
			2/ 5/24	5.5	8.9						
38	38	♂	8/ 3/22	5.4	...	40	3.8	4.0	36	....	Chronic nephritis; died 9/5
39	..	♂	11/21/23	5.1	...	55	5.6	7.0	53	....	Chronic nephritis; died 11/21
40	64	♂	4/20/23	4.8	...	30	5.5	4.7	..	....	Prostatic hypertrophy; operation; discharged improved 5/27
41	65	♀	10/29/23	4.7	8.6	98	5.1	6.6	64	7.36	Admitted 10/24 in coma due to cerebral arteriosclerosis; left hospital improved 1/16
			11/12/23	7.9	...	93	9.8	...	43	7.38	
			11/28/23	4.9	...	75	6.8	...	34		
			12/18/23	5.0	...	44	6.6				
			1/ 9/24	5.1	9.5	62	7.8				
42	53	♂	1/21/24	4.5	10.2	26	4.4	...	46	....	Cardionephritis
43	51	♂	6/21/23	4.4	...	38	3.1	4.3	54		Cardionephritis; discharged improved 7/19
			6/27/23	3.6	...	26	4.4	...	45		
44	50	♂	1/22/23	4.1	...	28	4.2	5.1	56	....	Chronic myocarditis; arteriosclerosis; discharged improved 2/5
			1/30/23	4.2	...	33					
45	56	♂	6/11/23	4.0	...	45	3.1	...	50	....	Prostatic hypertrophy; operation; discharged improved 5/27
			7/ 2/23	....	...	32	4.5	4.1	53		
46	65	♂	10/30/22	3.4	...	28	3.8	5.7	..	....	Cardionephritis; transferred to Bellevue
			11/ 6/22	3.4	11.5	25	3.0	4.5	42		
			11/21/22	3.3	...	29	3.9	3.8			
			12/ 4/22	3.8	...	29	4.0	...	52		
47	63	♂	11/21/23	3.6	...	77	3.6	...	43	....	Prostatic hypertrophy; died 11/21
48	59	♂	1/30/23	3.6	...	17	3.8	2.9	55	....	Urethral stricture; died 2/5
49	24	♂	4/17/23	3.6	9.3	26	2.6	5.3	61	....	Mitral stenosis; cardiac decompensation; left improved 6/7
			5/ 7/23	....	...	15					
50	45	♂	1/22/23	3.5	...	43	4.1	4.0	42	....	Tumor of bladder; died 3/27
			1/30/23	3.0	...	21					
51	50	♂	3/ 6/24	3.4	10.6	43	5.5	...	..	....	Extreme cardiac decompensation
52	41	♂	11/21/22	3.0	...	40	3.6	4.2	48	....	Nephrectomy following ruptured kidney; left improved 2/20/23
			11/28/22	....	...	64	5.6	...	60		
			12/ 5/22	....	...	21	3.0	...	53		
53	62	♂	10/25/22	2.3	10.0	51	5.1	4.5	34	....	Chronic mastoiditis; arterial hypertension; left improved 12/15
			10/30/22	2.4	...	25	3.3	5.4			
			11/10/22	2.3	...	13					
54	53	♂	1/30/23	2.3	...	17	3.5	3.4	62	....	Prostatitis; discharged improved 4/17

* In this table, ♂ indicates male; ♀, female.

sented in Table 1. In addition to figures for calcium and inorganic phosphorus, observations are recorded for the urea nitrogen, creatinin, uric acid, carbon dioxid capacity (or content), and in some instances for the p_H. In most of the severe nephritis cases it was possible to follow the progress of the condition by serial blood analyses. The cases have been arranged in order of the magnitude of the inorganic phosphorus.

METHODS

Little need be said regarding the analytic methods employed, since they are described in detail by one of us [11] elsewhere. However, as emphasis is being placed on the blood calcium and inorganic phosphorus the following comment may be made: The Briggs' modification of the Bell-Doisy method for inorganic phosphorus was used for the earlier determinations, but later the Benedict method was employed. With the Benedict method any hemolysis must be avoided, and for this reason serum was employed in the estimation of the inorganic phosphorus as well as for the calcium. The Clark method was used for the calcium, incorporating some of the suggestions of Tisdall for this determination.

COMMENT

The cause of the muscular twitchings and convulsions that occur in the terminal stages of chronic interstitial nephritis has been sought by various chemical researches during the last one hundred years. The term uremia doubtless originated from the observation made by Prevost and Dumas [12] in 1821 that extirpation of the kidneys gives rise to a marked accumulation of urea in the blood. Simple urea retention, however, has not been seriously considered as the cause of so-called uremic convulsions for many years, although as pointed out by Hewlett, Gilbert and Wickett [13] the administration of large doses of urea sufficient to raise the blood urea to a comparatively high figure may give rise to definite symptoms. The two other nitrogenous waste products, uric acid and creatinin, appear to be quite as devoid of toxic properties. In the case of creatinin retention, the possible formation of methyl guanidin needs to be considered, although there is as yet no definite evidence of such formation.

Can the muscular twitchings and convulsions of uremia be attributed to disturbances in the inorganic ions of the blood? Sodium and potassium are so constant in both normal and pathologic serums that they appear to be almost above suspicion in this connection. No special significance has been attached to the slight variations that occur in the magnesium. Since Binger [8] has shown that the injection of phosphates (acid, neutral or basic) into animals leads to a reduction in the blood calcium, this would seem to furnish the most plausible basis of explaining the lowering of the blood calcium in chronic interstitial nephritis. He has further pointed out that when basic and neutral phosphate salts are injected in quantity sufficient to lower the blood calcium tetany

11. Myers, V. C.: Practical Chemical Analysis of Blood, St. Louis, 1924.
12. Prevost, J. L., and Dumas, J. A.: Examen du sang et de son action dans les divers phénomènes de la vie, Ann. de chim. et phys. **23**:90, 1823.
13. Hewlett, A. W.; Gilbert, Q. O., and Wickett, A. D.: The Toxic Action of Urea in Normal Individuals, Arch. Int. Med. **18**:636 (Nov.) 1916.

results, but that tetany does not follow the injection of acid phosphate salts, despite the fact that the blood calcium is lowered by acid phosphate as well as by the basic or neutral salts. This doubtless explains why patients with chronic interstitial nephritis having blood calcium values below 7 mg. per hundred cubic centimeters do not show symptoms of tetany, since all such patients suffer from severe acidosis.[14] In other words we have a condition comparable to that produced in animals by the injection of acid phosphate salts. That the tetany resulting from the injection of phosphates is due to the reduction in the blood calcium, and not directly to the phosphate administration, would seem apparent from the fact that the tetany of parathyroid deficiency is due to a lowered blood calcium. Here the tetany is relieved by calcium administration and furthermore the inorganic phosphorus of the blood is essentially normal.

TABLE 2.—*Cases Having Convulsions or Serum Calcium Figures Below 7 Mg. or Both*

Case	Inorganic Phosphorus, Mg.	Calcium, Mg.	Convulsions	Urea Nitrogen, Mg.	Creatinin, Mg.	Carbon Dioxid, C.c.	Outcome
1	25.5	6.8	Yes	125	7.5	44	Died
2	20.2	9.5	None recorded	98	19.6	20	Died
3	18.2	6.9	Muscular twitchings	165	18.7	33	Died
4	17.4	...	None recorded	147	27.4	..	Died
5	16.4	3.8	Yes	106	25.0	37	Died
6	12.0	4.1	Yes	86	11.5	20	Died
7	14.4	6.9	Yes	139	21.0	27	Died
8	12.2	4.8	Yes	190	20.0	24	Died
9	12.2	6.5	No	155	13.4	35	Died
10	9.2	5.5	Yes	130	20.5	29	Died
11	11.9	...	Yes	111	10.2	20	Died
12	11.8	8.2	No	75	9.3	55	Died
16	5.8	7.0	Yes	40	6.5	62	Died
18	8.8	6.0	None recorded	158	20.0	41	Died
21	8.0	5.4	None recorded	172	11.5	..	Died
25	7.4	5.7	None recorded	83	5.2	35	Left hospital clinically improved
29	7.0	6.6	None recorded	60	9.0	31	Left hospital clinically improved

Our own data bearing on the possible relation of the blood calcium and phosphorus to the convulsive symptoms of terminal nephritis are summarized in Table 2. It will be noted that all of the first thirteen cases showing calcium values below 7 mg., with one exception, exhibited muscular twitchings, convulsions or both, while Cases 2 and 12 with blood calcium figures of 9.5 and 8.2 mg., respectively, did not show such symptoms. Attention should be called to the fact that the four less severe cases at the end of Table 2 did not disclose symptoms worthy of note despite the comparatively low calcium values. These cases were

14. Chace, A. F., and Myers, V. C.: Acidosis in Nephritis, J. A. M. A. **74**:641 (March 6) 1920.

under observation for a comparatively short length of time, however, and it is quite possible that the symptoms in question may have been missed. A study of our own data leads us to conclude, then, that a relatively high percentage of cases of terminal chronic interstitial nephritis, exhibiting muscular twitchings or convulsions, have serum calcium values below 7 mg.

The comments of de Wesselow [15] in this connection are of interest. He states:

> Apart from generalized convulsions, there are certain other nervous phenomena associated with uremia which may not improbably be related to the diminished content of the serum in calcium. These are the localized twitchings and general tremor which, though less striking symptoms than actual generalized convulsions, are certainly of worse prognostic import. In the material under discussion these symptoms were present in three patients, all of whom died. In all three the calcium of the serum had fallen to a lower figure than 7 mg. per hundred cubic centimeters, and in the patient who showed these symptoms in the most marked form the calcium content was the lowest of the series (Case 9). It is noticeable that in such cases the calcium may fall to a level at which symptoms of tetany might be expected to appear. Actually no such symptoms are found, nor are Trousseau's or Chvostek's signs present.

Both Binger [8] and Tisdall [16] have clearly demonstrated that there is a marked reduction in the serum calcium following the intravenous injection of phosphates. After the intravenous injection of dibasic sodium phosphate in dogs Tisdall found: (*a*) a reduction of the calcium from an average of 10.5 mg. per hundred cubic centimeters to 6.2 mg., and (*b*) an increase of the inorganic phosphorus from about 5 mg. per hundred cubic centimeters to an average of 19.0 mg. What is the relationship between the rise in inorganic phosphorus and the reduction of the serum calcium in the terminal stages of chronic interstitial nephritis? There is no uniform inverse relationship between the level of the inorganic phosphorus and the calcium in the different cases. This may be illustrated by Cases 1, 2, 5, 8, 12 and 15, for example. With inorganic phosphorus figures of 25.5, 16.4 and 12.2 mg., in Cases 1, 5 and 8, the calcium was 6.8, 3.8 and 4.8 mg., respectively, whereas in Cases 2, 12 and 15 with phosphorus figures of 20.2, 11.8 and 9.8 mg., the calcium was 9.5, 8.2 and 9.5 mg., respectively. However, in the individual cases one may note a gradual fall in the calcium with the rise in the inorganic phosphorus.

As pointed out by Chace and Myers [14] all patients with advanced chronic interstitial nephritis suffer from acidosis, and thus show low figures for the carbon dioxid capacity of the blood plasma. The most plausible explanation of the acidosis is that offered by Marriott and

15. De Wesselow (Footnote 9, first reference).

16. Tisdall, F. F.: The Influence of the Sodium Ion in the Production of Tetany, J. Biol. Chem. **54**:35 (Sept.) 1922.

Howland,[2] namely, that the acidosis is due to impaired ability to excrete acid phosphate. How well then can the figures for the carbon dioxid capacity of the plasma be correlated with those for the inorganic phosphorus? The data recorded in Table 1 indicate that low figures for the plasma bicarbonate may be present in the absence of high figures for the inorganic phosphorus, but that cases showing high figures for the inorganic phosphorus are almost invariably accompanied by low figures for the carbon dioxid capacity of the plasma. In six of these patients (all the patients examined who did not receive alkali) the p_H of the blood plasma showed that the acidosis was definitely uncompensated.

TABLE 3.—*Comparison of the Prognostic Value of Inorganic Phosphorus and Creatinin of the Blood in Nephritis*

Case	Inorganic Phosphorus, Mg. to 100 C.c.	Creatinin, Mg. to 100 C.c.	Outcome	Case	Inorganic Phosphorus, Mg. to 100 C.c.	Creatinin, Mg. to 100 C.c.	Outcome
1	25.5	7.5	Died	28	6.3	5.0	Died
2	20.2	19.6	Died	29	7.0	9.0	Clinically improved
3	18.2	18.7	Died	30	6.0	11.1	Died
4	17.4	27.4	Died	31	5.9	4.1	Clinically improved
5	17.2	25.0	Died	32	5.9	8.4	Died
6	15.2	12.4	Died	33	8.5	9.2	Clinically improved
7	14.4	21.0	Died	34	5.7	5.0	?
8	13.9	20.0	Died	35	6.3	7.9	Clinically improved
9	12.2	13.4	Died	36	5.5	4.8	Clinically improved
10	11.9	20.3	Died	37	5.5	...	Clinically improved
11	11.9	10.2	Died	38	5.4	3.8	Died
12	11.8	9.3	Died	39	5.1	5.6	Died
13	11.3	....	Died	40	4.8	4.7	Clinically improved
14	11.1	14.4	Died	41	7.9	9.8	Clinically improved
15	9.8	14.0	Died	42	4.5	4.4	?
16	9.3	9.6	Died	43	4.4	4.4	Clinically improved
17	11.0	15.0	Died	44	4.2	4.2	Clinically improved
18	14.3	20.0	Died	45	4.0	4.5	Clinically improved
19	9.2	11.0	Died	46	3.8	4.0	Left hospital
20	8.7	11.5	Died	47	3.6	3.6	Died
21	8.0	11.5	Died	48	3.6	3.8	Died
22	7.7	8.6	?	49	3.6	2.6	Left hospital
23	8.2	14.2	Clinically improved	50	3.5	4.1	Died
24	7.5	7.2	?	51	3.4	5.5	?
25	7.4	5.2	Clinically improved	52	3.0	5.6	Left hospital
26	8.7	8.3	Died	53	2.3	5.1	Left hospital
27	6.6	4.4	?	54	2.3	3.5	Left hospital

A number of the patients received sodium bicarbonate as may be noted in Table 1 under Remarks, or by the sudden rise in the figures for the carbon dioxid capacity. It has obviously been necessary to disregard these figures in formulating our conclusions regarding the relationship between reduction of the carbon dioxid capacity and the rise in the inorganic phosphorus.

Owing particularly to the question that has been raised as to the identity of the chromogenic substance formed in blood filtrates by picric acid and alkali, de Wesselow [15] advocates the use of the inorganic phosphorus as a prognostic sign superior to the blood creatinin. In order to compare the blood creatinin with the inorganic phosphorus in the present series of cases, single determinations of these constituents

are retabulated for each of the cases in Table 3. In this particular table there appears to be little difference between the two determinations from a prognostic point of view. Unfortunately a number of the less severe cases were not followed after the patients left the hospital. There is little doubt about the reliability of inorganic phosphorus retention as a prognostic sign, but the creatinin is equally reliable and the retention appears to occur a little earlier than in the case of the phosphorus. Since the publication of our final paper [17] on the prognostic value of the blood creatinin in nephritis in 1919, we have compiled observations on several hundred cases, and have yet to encounter a case at variance with our original conclusion, that in cases in which the creatinin rises above 5 mg. per hundred cubic centimeters of blood the patients rarely show any marked improvement and almost invariably die within a comparatively limited time, the only exception being in cases in which the retention is due to some acute renal condition.

CONCLUSIONS

A relatively high percentage of cases of chronic interstitial nephritis with muscular twitchings or convulsions show values for the calcium of the blood serum below 7 mg. per hundred cubic centimeters.

There is no uniform inverse relationship between the level of the inorganic phosphorus of the serum and the calcium in different cases. In other words the retention of phosphorus has a greater influence in some cases than in others. However, in individual cases one notes a gradual fall in the calcium with a rise in the inorganic phosphorus.

Low figures for the carbon dioxid capacity of the plasma may be present in the absence of high figures for the inorganic phosphorus, but cases showing high figures for the inorganic phosphorus are almost invariably accompanied by low figures for the carbon dioxid capacity of the plasma. Here the few observations recorded for the p_H indicate that the acidosis is generally of the uncompensated variety.

There is little doubt about the reliability of inorganic phosphorus retention as a prognostic sign in chronic nephritis, but the creatinin is equally reliable and the retention appears to occur a little earlier than is the case with the inorganic phosphorus.

17. Myers, V. C., and Killian, J. A.: The Prognostic Value of the Creatinin of the Blood in Nephritis, Am. J. M. Sc. **157**:674 (May) 1919.

ACUTE FEBRILE ANEMIA*

A NEW DISEASE?

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At the present stage of medical progress one hesitates to present new clinical syndromes. However, the case here described presents a picture that, to my knowledge, does not correspond with any known clinical entity.

REPORT OF CASE

C. E., an unmarried woman, aged 38, of good family and personal history, was seen by me for the first time May 7, 1925. The present illness was of two weeks' duration and began as an "attack of biliousness" characterized by vomiting, malaise and a feeling of weakness. The vomitus consisted of bile stained food and contained no blood. A few days later she developed nosebleed and severe pain in the occipital region. At this time her sister, who is a trained nurse, came to take care of her. She found the patient extremely ill, presenting a peculiar dark, glassy, "tobacco" color, with little brown spots in various parts of the body and a temperature of 101 F. Within the following day or two the patient sank very low, becoming listless and picking at the bed clothes. Her color gradually became pale and a generalized edema developed. There were several attacks of severe pain in the region of the spleen; these came on suddenly and lasted several hours each time.

A blood count, April 30, 1925, showed 27 per cent hemoglobin (Dare); 1,250,000 red cells; 5,750 white cells, with 61 per cent neutrophils, 36 per cent lymphocytes, 2 per cent eosinophils, and 1 per cent basophils. One week later, on the day of my first examination, the hemoglobin was so low that it was not possible to make an accurate reading, probably about 15 per cent. The erythrocytes numbered about 1,000,000, and the leukocytes about 5,000, with a differential count essentially the same as in the previous examination. Blood cultures taken three times at three day intervals were consistently sterile. The urine, on several examinations, showed a trace of albumin and a moderate number of pus cells. A stool examination revealed nothing of note. The gastric contents showed a total absence of free hydrochloric acid. Roentgen-ray examination of the lungs showed irregular shadows that were interpreted as patches of congestion or of bronchopneumonic consolidation.[1]

The general condition of the patient seemed hopeless. There was a deathlike pallor, numerous petechial spots, and a glassy edema involving the entire body. There was no jaundice. The patient was in a stupor, with labored respiration of the sighing type. The tongue was swollen and ashy gray. The heart action was feeble; the lungs appeared to be flooded with edema. The liver and spleen appeared moderately enlarged to percussion, but neither organ could be felt under the ribs. The temperature varied between 100 and 101 F. during most of the time, with an occasional rise to 103. The pupils were dilated and reacted sluggishly to light; the knee and ankle jerks could not be obtained.

Shrinking from the idea of giving up without a fight, I suggested the use of blood transfusions, although I had no hope of recovery. A universal donor was secured and 300 cc. of whole blood was transfused by the syringe method at the

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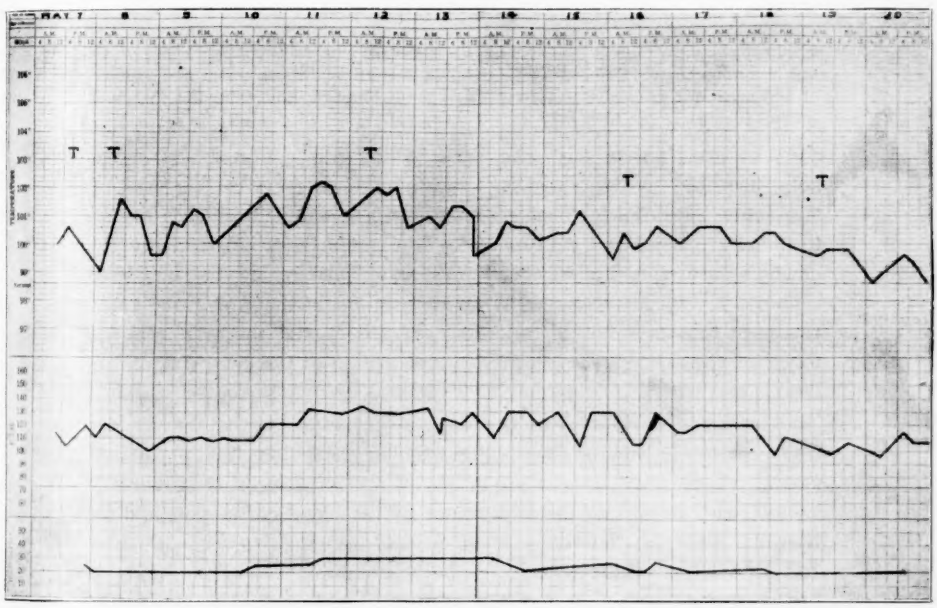
1. A more recent roentgenographic examination of the chest showed the lungs to be entirely clear.

patient's bedside. Surprising improvement in the patient's general condition followed. The procedure was then repeated and, in all, ten transfusions were performed between May 7 and June 12. The amount of blood given varied from 300 to 500 cc., and the intervals between transfusions varied from one day to one week. The patient showed a marked and steady improvement. The blood rose steadily, so that within a week after the last transfusion a practically normal count was obtained. By the end of June the patient was up and around enjoying normal health.

In addition to the transfusions the patient received daily ultraviolet (Alpine) radiations. At this time it cannot be definitely stated whether or not the radiations played any part in the patient's remarkable recovery.



Temperature, pulse and respiration curves in case reported: *T*, dates on which first five blood transfusions were given.

COMMENT

From the outset, it was evident that I was dealing with a hitherto undescribed disease. A careful search of the literature revealed only a single instance in which a case is reported resembling the one described here.[2]

The patient was a man, aged 26, admitted to the Prince Alfred Hospital, Sydney, Australia, Dec. 17, 1901. His illness was of five weeks' duration and began with "sore throat and toothache." He apparently recovered from both these complaints in a few days, but continued to grow weaker, suffered from

2. Macintosh, A. H., and Cleland, J. B.: A Case of Rapidly Increasing Anemia with Irregular Pyrexia and Death, Australasian M. Gaz. **21**:462 (Sept. 20) 1902.

frontal headache, and rapidly became anemic. On examination he was found not emaciated, but pale and "lemon yellow." There was no jaundice. The blood examination on admission showed a hemoglobin of 26 per cent; red cells, 1,415,000; white cells, 14,000. The differential count is not reported, except for the statement that there were a large number of large leukocytes with neutrophil protoplasm granules. The shape of the red cells remained unaltered. The patient grew steadily weaker and twelve days after admission the blood examination showed red cells, 710,000; white cells, 20,000. The patient died the next day.

The postmortem examination revealed lesions usually seen in severe anemia including a "few small petechiae and vibices under the visceral pericardium" and a number of large bronchopneumonic patches in the lungs. Commenting on their case, the authors state: "This case, in its clinical and postmortem appearances, would seem to occupy a position midway between various forms of septicemia and pernicious anemia. It resembles the former in the raised temperature, in the bronchopneumonia, the petechiae and tendency to hemorrhages, the leukocytosis and the enlarged soft spleen; the latter, in the great diminution in the number of red cells, the clinical characteristics of a profound anemia, and the increased amount of iron in the liver."

While this article was being prepared for publication, I was agreeably surprised by Moschcowitz's [3] illuminating report on his case of "an acute febrile pleiochromic anemia, with hyaline thrombosis of the terminal arterioles and capillaries." The resemblance between Moschcowitz's case, the case of Macintosh and Cleland, and the one here reported is indeed striking. It appears probable that the three cases represent the same morbid condition. If this is true, the three reports, together, constitute a fairly complete description of the clinical manifestations and pathologic anatomy of a hitherto unknown disease.

The essential features of this disease appear to be: a more or less acute onset; a rapidly developing anemia resembling the pernicious variety of severity but retaining the characteristics of a secondary anemia with respect to the appearance of the blood corpuscles, and an irregular pyrexia, the temperature usually ranging between 100 and 102 F. The characteristic pathologic lesion, as described by Moschcowitz, is a plugging of the terminal arterioles or capillaries with hyaline thrombi. In a more advanced stage these hyaline masses are penetrated by fibroblasts and a "tubercle-like structure is formed."

Therapeutically, blood transfusions given in small amounts and at frequent intervals proved successful in one instance.

No light, however, is shed on the etiology of this strange disorder. The general clinical course is strongly suggestive of an infection, but blood cultures in two instances remained sterile. No mention is made of postmortem bacteriologic studies in Moschcowitz's case, except the statement that no bacteria were found in the tissues. Macintosh and

3. Moschcowitz, Eli: An Acute Febrile Pleiochromic Anemia with Hyaline Thrombosis of the Terminal Arterioles and Capillaries, Arch. Int. Med. **36**:89 (July) 1925.

Cleland obtained a growth of a "large bacillus with rounded ends and irregular staining" from the spleen examined fourteen hours after death. No blood cultures were made during life. It is hoped that the future may afford opportunity for the solution of this phase of the problem.

CHANGES IN RESPIRATION, IN CIRCULATION AND IN THE COAGULATION TIME OF BLOOD PRODUCED BY SODIUM CITRATE INJECTIONS

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In a recent study of the toxicity of sodium citrate on exsanguinated dogs we noticed abnormal variations of the coagulation time of the blood.[1] About this time Neuhof and Hirshfeld[2] published a paper asserting that intramuscular injections of sodium citrate in doses of 30 cc. of 30 per cent solution for 150 pounds (68 Kg.) would decrease the coagulation time of the blood. So sure were these observers of their results that they advised the use of sodium citrate as a matter of routine in cases of actual or impending hemorrhage. In view of the fact that sodium citrate ordinarily is regarded as an anticoagulant, a careful study of this phenomenon was attempted.

It has been generally accepted that the citrate and oxalate group of anticoagulants affect the blood calcium so that it does not perform its essential share in the process of coagulation. Oxalates are anticoagulants because they precipitate the blood calcium, thus rendering it inert in the presence of conditions that promote coagulation of the blood. The action of sodium citrate is less clearly understood because of its complex formula. Bloch[3] and Mathews[4] suggest that sodium citrate renders the blood calcium nonionizable (although in solution) and thus prevents its activity during coagulation. That the blood calcium is affected by the sodium citrate is shown by the fact that if the proper amount of calcium were added to incoagulable citrated blood, it will coagulate promptly.

It is beyond the scope of this article to discuss theories relating to the coagulation of the blood. This has been done extensively by most workers on the coagulation of the blood. The work of Hewson,[5]

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1. Joannides, M., and Cameron, A. L.: Citrated Blood Transfusions: An Experimental Study of the Toxicity of Sodium Citrate in Exsanguinated Dogs, J. A. M. A. **82**:1187-1189 (April 12) 1924.

2. Neuhof, H., and Hirshfeld, S.: Intramuscular Administration of Sodium Citrate: A New Method for the Control of Bleeding, Ann. Surg. **76**:1 (July) 1922.

3. Bloch, M.: A Study of the Autocoagulant Action of Sodium Citrate and the Part Played by Calcium in the Blood, Lancet **2**:301 (Aug. 7) 1920.

4. Mathews, A. P.: Physiological Chemistry, New York, William Wood & Co.

5. Hewson, W.: The Works of William Hewson, London, Sydenham Society.

Wooldridge,[6] Morawitz,[7] Howell,[8] and Mills and Guest [9] gives a fairly clear conception of the theoretical application of various findings in blood coagulation. Loucks,[10] of the laboratory of physiology at the University of Minnesota, carried out an extensive series of experiments to determine the various factors involved in the coagulation of the blood. He found that calcium is absolutely necessary throughout the entire process of coagulation. It is necessary for the formation of thrombin. Calcium must be present for thrombin to act on fibrinogen. In other words, a calcium-free thrombin would not coagulate fibrinogen or blood. The work of Loucks disproves the theory of Mills and Guest [9] that tissue fibrinogen unites with blood fibrinogen to form fibrin. They assert that in this process calcium acts as a connecting link. He found that calcium is necessary for the reaction to go on. Calcium was present in the final product but not as a chemical constituent of the fibrin molecule, because it could be easily washed out with water. It is possible that the so-called thrombin is a tissue fibrinogen complex, because Loucks found that calcium could be dialyzed neither from thrombin nor from tissue fibrinogen but that it could be removed by oxalic acid. This indicates that the calcium is in some way bound to the tissue fibrinogen and thrombin. Furthermore, he could not produce an active thrombin from calcium-free fibrin. The work of Loucks proves that calcium is absolutely necessary to all stages of blood coagulation and perhaps it acts only as a catalyst. On the basis of these facts, therefore, one would expect that sodium citrate would decrease the coagulability of the blood because, as Bloch [3] suggests, it renders the blood calcium nonionizable and thus prevents either the first or second stage of coagulation.

TECHNIC

If one searches through the literature for an accurate method for determining the coagulation time of the blood, he will find descriptions of an innumerable number of methods. Hinman and Sladen [11] and,

6. Wooldridge, L. C.: Croonian Lecture on the Coagulation of the Blood, in: On the Chemistry of the Blood, and Other Scientific Papers, London, 1893; Further Observations on the Coagulation of the Blood, J. Physiol. **4**:226, 1882; The Coagulation Question, J. Physiol. **10**:329, 1889.

7. Morawitz: Beitr. z. chem. Phys. u. Path. **4**:381, 1903; Deutsch. Arch. f. klin. Med. **79**:1; 215, 1904; Beitr. z. chem. Phys. u. Path. **5**:133, 1904.

8. Howell, W. H.: The Harvey Lectures, Philadelphia, 1916-1917, Series 12, p. 292; Prothrombin, Am. J. Physiol. **35**:474, 1914.

9. Mills, C. A., and Guest, G. M.: The Rôle of Tissue Fibrinogen (Thrombokinase) in Fibrin Formation and Normal Clotting, Am. J. Physiol. **57**:395 (Oct.) 1921.

10. Loucks, M. M.: Thesis for Master of Science Degree, Submitted to the University of Minnesota, 1925.

11. Hinman, F., and Sladen, F. J.: Measurement of the Coagulation Time of the Blood and Its Application, Bull. Johns Hopkins Hosp. **33**:207, 1907.

later, Solis Cohen [12] give a complete review of the various methods used. In the majority of these methods the blood was removed either by puncturing the skin and squeezing out blood, thus bringing it in contact with the tissues, or by means of venipuncture. In the latter case the blood was manipulated considerably and a great portion of it came in contact with a foreign body, such as the surface of a small gage needle, during the process of removal. In view of the fact that we could cut down to the vein or artery of the dogs, we inserted short and fairly wide glass cannulas and allowed the blood to be received in our centrifuge tubes. We used graduated centrifuge tubes of uniform size and shape for our receptacles. These were cleaned with bichromate cleansing solution, then with distilled water, and finally with alcohol and ether before they were sterilized in the autoclave. A piece of cotton was inserted at the mouth of the tube just before the sterilization, and thus both moisture and dust were excluded from the tube. The blood was removed from the blood vessel by inserting a sterile, right angle, small glass cannula into the lumen of the exposed vessel. The cannulas were cleaned and dried in the same manner as the tubes. A new cannula was used for each determination. Care was taken not to allow the blood to come in contact with any tissues. In order to avoid the possibility of using stagnant blood, which perhaps may be undergoing changes of coagulation, we allowed a few cubic centimeters of blood to run out of the vessel and then took a series of samples. At least two tubes were used for each determination and the interval between these samples was only from five to ten seconds. We used from 2 to 5 cc. of blood for each of our samples. After the cannula was removed the tissues were wiped clean and covered with sterile gauze. Care was taken not to allow any bubbles to get into the tubes. Those containing air bubbles were discarded. The tubes were kept in the palm of the hand and an attempt thus made to keep the blood as nearly as possible at body temperature. The tubes were tilted carefully and individually and thus the film on the surface was not broken. If the film was broken, the coagulation time was invariably prolonged. A series, five or more, of groups of normals was taken before the experimental procedure was begun. All our animals were kept under light ether anesthesia.

In our experiments the coagulation time was the time interval from the moment the blood left the vessel until a film appeared on the surface and was thick enough so that on inverting the tube the blood did not run out.

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12. Solis Cohen, Myer: The Coagulation Time of the Blood as Affected by Various Conditions, Arch. Int. Med. **8**:684 (Nov. 1) 1911; **8**:20 (Dec.) 1911.

EXPERIMENTS AND RESULTS

In the first series of experiments we studied the effect of intramuscular injections of sodium citrate solution on the coagulation time of the blood. All the animals were kept under light ether anesthesia. No preliminary medication was given. Seven experiments were performed on dogs.

In one experiment 10 cc. of a 2 per cent solution of sodium citrate was injected into a dog weighing 55 pounds (24.9 Kg.). The trisodium citrate was used because, as Mellon [13] and his co-workers described, the monosodium citrate and the disodium citrate are a possible source of toxic reactions because of their variations in the hydrogen ion concentration. In their experience the trisodium salt was the least toxic. Samples of blood were taken at ten minute intervals for one hour after the injections. The coagulation time before and after the experiment varied within the same limits. In the remaining six experiments a 30 per cent fresh solution of trisodium citrate was used. In three of these there was a slight and very transitory lengthening of the coagulation time of the blood, from about ten to fifteen minutes after the injection. In the remainder the coagulation time was within normal limits. Five experiments were performed on patients who had no apparent blood disease. In all but one, the coagulation time was much the same before and after the injection of 30 per cent sodium citrate solution into the gluteal muscles. In one patient the coagulation time dropped from nine minutes and forty-seven seconds to two minutes and thirty-five seconds, and was as low as five minutes and thirty seconds when determined six hours after the injection. Two samples were taken each time but not more than three determinations were made on each patient after the injection. The blood was drawn through a 20-gage needle into a syringe and then emptied into the sampling tube. Just what happened to cause a decrease in one and no change in the rest we cannot tell. The technic used in the patients was the same as that used by Neuhof and Hirschfeld,[2] with the exception of the use of procain for producing local anesthesia. This part was omitted because we did not desire to bring in any more sources of error than absolutely necessary. All the patients complained of severe pain at the site of injection. No toxic symptoms were noticed.

In another series of experiments the intravenous injection of trisodium citrate was studied. Various concentrations were injected. In one experiment five injections, 10 cc. each, of a 2 per cent solution of citrate, were made on a dog weighing 26 pounds (11.8 Kg.). No toxic effects were noticed, and the variations in the coagulation time were within the normal. Samples were taken from five to fifteen

13. Mellon, R. R.; Hastings, W. S., and Casey, Gertrude: Observations on the Effect of Sodium Citrate on the Blood, J. A. M. A. **77**:1678 (Nov. 11) 1923.

minutes after each injection. Sodium citrate was injected at fifteen minute intervals. Our negative results made us consider the possibility of not injecting a sufficient amount of sodium citrate to cause any appreciable change in the coagulation time of the blood. We tried, therefore, larger amounts and greater concentrations for our subsequent doses.

Five experiments were performed with intravenous injections of a 10 per cent solution of citrate. Two dogs died within a few minutes after the injection, while the other three passed through a period of respiratory and circulatory depression, and finally recovered spontaneously. In all these animals the coagulation time did not change materially after the injection. When greater concentrations were used, the amounts had to be diminished accordingly. In three animals a 20 per cent solution of citrate was used. One dog, weighing 14.5 pounds (6.6 Kg.), after the injection of a 5 cc. of a 20 per cent solution, almost instantly developed a general convulsion with marked opisthotonos and incontinence of urine. The respiratory movements stopped. The pulse was not palpable. About forty seconds after the onset of these symptoms the dog took a few gasping breaths and the pulse could now be palpated. It was 140 beats per minute. One minute later there was a complete return to normal. Samples of blood were not taken during the acute symptoms. Two minutes and sixteen seconds after the injection the coagulation time was within normal limits. At this time the animal was completely relaxed and breathed normally. Ten minutes later, while the animal was apparently in good condition, an injection of 10 cc. of a 20 per cent solution of citrate was given intravenously. The respirations stopped instantly and permanently. The heart beat was slowed down from 140 to 60 per minute. The heart continued to beat for fourteen minutes and three seconds after the beginning of the last injection. No coagulation time determinations were made at this time.

In the second experiment two toxic doses of 5 cc. of a 20 per cent solution were given to a dog weighing 34 pounds (15.4 Kg.). The symptoms produced were those of circulatory and respiratory collapse with convulsions. In this animal the symptoms persisted for 147 seconds. When the dog was apparently normal again a third and fatal dose, consisting of 10 cc. of 20 per cent sodium citrate, was given. The blood assumed a peculiar purple and became incoagulable so that it could be siphoned out by attaching a cannula to the vessel and connecting the cannula to a tube leading down to a point below the level of the table. Blood pressure and respiration determinations were made on this dog. Physiologic sodium chlorid solution was used as the pressure fluid. The systolic pressure dropped from 113 to 8 mm. of mercury. The respirations became so shallow that it was impossible to record them on the kymograph. After the last injection,

the systolic pressure remained at the level of 8 mm. of mercury for sixty seconds. It then suddenly rose to 160 mm. of mercury, and after remaining close to that level for twenty-five seconds it gradually dropped to zero. In the third experiment a fatal dose of 10 cc. of a 20 per cent solution of sodium citrate was given to a dog weighing 29.5 pounds (13.4 Kg.). The usual toxic findings appeared, and were followed by death. At times there is a transitory stimulation of respiration preceding the depression. Our results correspond quite closely to those obtained by Salant and Kleitman,[14] who found a fall in the arterial pressure. Similar results have been obtained by Love.[15] He found that 50 mg. of citrate per kilogram given intravenously to small or medium sized dogs caused a depression of the heart and of the blood pressure. The blood pressure rose to normal or a few millimeters above normal at the end of a minute. Larger doses caused a sharper final rise of the blood pressure.

Much the same results have been obtained in a series of fourteen experiments in which intravenous injections of 30 per cent citrate solution were made. Realizing that there must be a definite association between the changes in coagulation and the acute toxic symptoms, we attempted to determine the coagulation time of the blood at the height of the toxic manifestations. Blood taken during this time was found to remain incoagulable for forty-eight hours after the injection. On the other hand, as the symptoms subsided the samples would show variations close to normal coagulation time. We assumed, therefore, that something happens to the blood or tissue calcium to cause convulsions and changes in the coagulation of the blood. Calcium chlorid was used, therefore, to counteract the effect of citrate. In one case 20 cc. of 30 per cent calcium chlorid was injected thirty seconds after the injection of 10 cc. of 30 per cent sodium citrate. There was an immediate and complete relaxation of the animal without any more convulsions. The respirations now became deeper and regular. During the acute symptoms samples of blood showed no coagulation for forty-eight hours. On the other hand, immediately after the injection of calcium and the subsiding of toxic symptoms the blood coagulated within the normal limits. The unusual effect of the calcium injection was that the animal, which weighed only 31 pounds (14.1 Kg.), received a total of 66 cc. of 30 per cent solution, or 19.8 Gm. of sodium citrate, and did not die.

In view of the fact that very acute symptoms developed with great concentrations of the citrate, we attempted to study the cumulative

14. Salant, W., and Kleitman, N.: Studies on the Pharmacology of Sodium Citrate: I, The Influence of Sodium Citrate on Respiration and Circulation, J. Pharm. & Exper. Therap. **20**:481 (Jan.) 1923.

15. Love, G. R.: Studies on the Pharmacology of Sodium Citrate on the Circulation, J. Lab. & Clin. Med. **9**:175 (Dec.) 1923.

effect of citrate injections on the coagulation time. A 2 per cent solution was used and was injected intravenously from a buret at a constant rate. The animal that weighed 17 pounds (7.7 Kg.) was apparently normal until 200 cc. of the solution was injected. From then on the respirations became shallower and slower till they stopped, when 300 cc. was injected. When 280 cc. of citrate was injected samples of blood did not coagulate for forty-eight hours. They were kept at room temperature and discarded after forty-eight hours. This experiment shows quite emphatically that both the amount of sodium citrate and the concentration of the solution must be carefully considered.

Seven experiments were performed to determine the effect of intravenous injections of 0.2 per cent sodium citrate solution injected in combination with 0.75 per cent sodium chlorid solution. In all these experiments there was a definite but transitory decrease in the coagulation time of the blood. The coagulation time returned to normal within an hour. The greatest coagulability was noticed within from three to five minutes after the injection of quantities of from 250 to 400 cc. of the combined solution. When sodium chlorid alone was injected we found no deviation from the normal.

Small, repeated hemorrhages, produced, for instance, by taking several samples of blood, had no appreciable change on the coagulation time of the blood. Sudden hemorrhages in which amounts of from 250 to 300 cc. of blood were removed showed a definite decrease in the coagulation time of the blood. This decrease in time became even more pronounced when the blood was reinjected as a 0.2 per cent citrated blood solution. The return to normal was prompt in all cases. Four such experiments were performed with uniform results.

Samples of blood were taken from the artery and from the vein to determine possible differences in the coagulation time of the blood. In two such experiments there was no appreciable difference between the two sources.

Salant and Wise [16] made careful determinations of the fate of sodium citrate in the blood and in the urine. By using a modification of Deniges' test they found that sodium citrate disappears rapidly from the circulation after intravenous injections into dogs and into cats. No sodium citrate is found in the urine when doses under 0.5 Gm. per kilogram are given intravenously. Sodium citrate was evidently eliminated rapidly in our dogs because the animals recovered quite promptly. We had a similar experience in the case of a patient who had gangrene of his toes secondary to polycythemia vera. On the basis of Willy Meyer's [17] report, the house officer injected large doses of

16. Salant, W., and Wise, L. E.: The Action of Sodium Citrate and Its Decomposition in the Body, J. Biol. Chem. **28**:27 (Dec.) 1916.

17. Meyer, Willy: The Conservative Treatment of Gangrene of the Extremities Due to Thrombo-angiitis Obliterans, Ann. Surg. **63**:280 (March) 1915.

sodium citrate intravenously. Willy Meyer reported satisfactory results when this salt was used in connection with systematic infusion of Ringer's solution. This patient received nine intravenous injections of a 3 per cent watery solution of sodium citrate. The amounts used varied from 300 to 450 cc. of a 3 per cent solution. Studies on the coagulation time showed no appreciable change from the normal. This patient weighed 147 pounds (66.7 Kg.). We were present during one of these injections. We noticed that when he received about 200 cc. of the solution he volunteered the statement that he felt "funny." By this he meant that he had dimness of vision and a sense of constriction in his head. For a few moments he was apparently unconscious because he did not respond to questions nor did he know of the questions when asked about them at a later time. At the beginning of the injection the pulse rate was 120 beats per minute. During the acute symptoms it became only 80 per minute. As soon as the injection was stopped the symptoms disappeared very promptly. Unfortunately, the injections of sodium citrate did not improve the gangrene. We agree with Cheinisse [18] who warns against the indiscriminate use of sodium citrate. This drug is dangerous when used in large doses but useful in smaller doses, such as those used for transfusion purposes. Fortunately, it is eliminated very promptly, so that even with large doses the patient may have a chance to recover spontaneously.

SUMMARY AND CONCLUSIONS

1. Our studies on man and on the dog show that the injections of sodium citrate do not usually increase the coagulability of the blood.

2. Intramuscular injections are less dangerous than intravenous injections.

3. A 3 per cent solution of sodium citrate, which is isotonic with blood, has been fairly well tolerated by a patient who received from 300 to 450 cc. intravenously. This practice, however, should be discouraged.

4. Intravenous injections of great concentrations of sodium citrate are dangerous because they cause immediate respiratory and circulatory collapse.

5. Calcium chlorid given promptly during the height of toxic symptoms may save the animal from death. But calcium chlorid itself is a dangerous drug if injected intravenously in large doses.

6. The toxic symptoms must in some way be associated with changes that concern the coagulation of the blood, because the latter becomes incoagulable under these conditions. As soon as the toxic symptoms subside the coagulation time of the blood becomes normal.

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18. Cheinisse, L.: Le Citrate de soude dans le traitment des affections vasculaires, Presse méd. **30**:258 (March 25) 1922.

7. Shallow, slow breathing, a rapid and later slow pulse rate, convulsions, at times salivation and incontinence of urine, with a drop in the systolic pressure and increased coagulation time, mark the presence of toxic effects of sodium citrate.

8. Small, repeated hemorrhages apparently have no effect on the coagulation time. On the other hand, when larger amounts of blood are removed they cause an increased coagulability of the blood. Citrated blood transfusion under such conditions increases the coagulability of the blood still more.

9. There is no apparent difference in the coagulation time of the arterial and of the venous blood.

10. Injections of 0.2 per cent sodium citrate solution in a 0.75 per cent sodium chlorid solution invariably decrease the coagulation time of the blood and cause no toxic symptoms if the citrate dose is within the subtoxic limits.

11. Sodium citrate apparently disappears from the blood stream promptly since the toxic symptoms produced by the salt disappear quite promptly.

12. Sodium citrate used in amounts corresponding to those for blood transfusion is a useful drug. In larger amounts or concentrations it is a dangerous drug.

TESTING OF LIVER FUNCTION

I. DETOXICATION BY THE LIVER *

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The liver, our largest gland, has numerous and varied functions, and hence a most complex physiology. It plays an important rôle in the metabolism of carbohydrates, proteins and fats; it forms bile salts and helps form and excrete bile pigments; it modifies various substances produced in the body in such a way as to make these substances more easily handled and less harmful to the body; it performs detoxication work.

An exact determination of the condition of the liver in any normal or pathologic case would, of course, presuppose a complete understanding of its performance of all these functions. But since this is quite impracticable, one would rather attempt the study of merely one or two functions, which while sufficiently easy of determination, and this by a test not too cumbersome for manipulation, would yet give a fairly good estimate of the general functional condition of the organ. Several such tests have been tried but none has proved completely satisfactory. We shall attempt to add another contender to these liver function tests.

A study of the chemical defense mechanism of the animal body has shown that although in general definite processes of detoxication are by no means specific for the various animals, yet certain chemical and metabolic reactions may at times be limited to a single species. One of the best known differentiations of this kind is the detoxication of benzoic acid in the avian body by ornithine,[1] while in the other animals the amino-acid glycocoll[2] is employed. A still more interesting case, as shown by one of us, is the use of another amino-acid, glutamine (by the human being only), in the detoxication of an acid produced during intestinal putrefaction.[3] In this one reaction at least the process occurring in the human body is entirely different from the method in which this same putrefaction product is handled by the lower animals.

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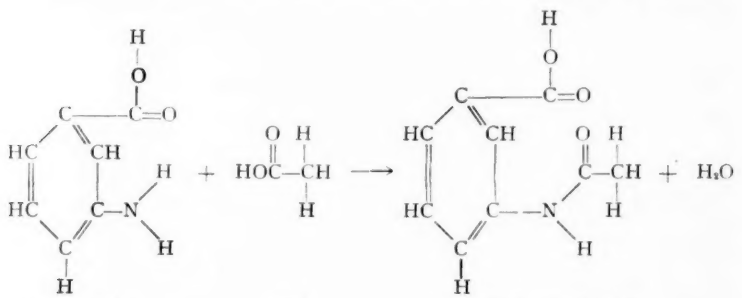
* From Harlem Hospital and the chemical research laboratory of Fordham University.

1. Jaffé, M.: Ber. d. deutsch. chem. Gesellsch. **10**:1925, 1877.
2. Woehler, F.: Ztschr. f. physiol. Chem. **1**:125, 1824.
3. Thierfelder, H., and Sherwin, C. P.: Ber. d. deutsch. chem. Gesellsch. **47**:2630, 1914.

It has been pointed out in a previous article [4] that the defense against foreign organic molecules is maintained by the use of seven or eight general reactions. We were surprised some time ago to find that acetic acid when used by the animal body as a defense against amino compounds is not limited to one or two aliphatic compounds and to the side chain amino groups of two or three aromatic substances, but is employed by the normal human body [5] in the detoxication of certain aniline derivatives in which the amino group is firmly bound to the benzene ring.

Salkowski [6] described the feeding of meta-aminobenzoic acid to a dog, after which he recovered from the urine two compounds that he believed to be uraminobenzoic acid and aminohippuric acid, the former a union of the meta-aminobenzoic acid through its amino group with urea, and the latter a combination through the carboxyl or acid group with glycocoll. While these reactions in vivo seemed most logical, the yields of the compounds isolated by him were most unsatisfactory and the analyses also were none too convincing. A number of years later it was found by Cerecedo and Sherwin [7] that para-aminophenylacetic acid, the homolog of Salkowski's compound, when fed in varying doses, was always detoxicated by the dog through a union with glycocoll, while by the human being and rabbit it was excreted as a combination with acetic



meta-amino-benzoic acid | acetic acid | meta-acetylamino-benzoic acid

acid. As Salkowski had described but a single reaction in the case of human beings, dogs and rabbits, it was decided to repeat the work on meta-aminobenzoic acid. Subsequent work by Muenzen, Cerecedo and one of us [8] showed that meta-aminobenzoic acid when fed to a dog was

4. Sherwin, C. P.: Physiol. Rev. **2**:238 (April) 1922.

5. Muenzen, J. B.; Cerecedo, L. R., and Sherwin, C. P.: Proc. Am. Soc. Biol. Chem. **19**:16, 1925.

6. Salkowski, E.: Ztschr. f. physiol. Chem. **7**:93, 1882.

7. Cerecedo, L. R., and Sherwin, C. P.: J. Biol. Chem. **62**:217 (Nov.) 1924.

8. Muenzen, J. B.; Cerecedo, L. R., and Sherwin, C. P.: Unpublished data.

largely excreted unchanged, only traces of a glycocoll compound (meta-aminohippuric acid) being found. When the meta-aminobenzoic acid was fed to human beings and rabbits, however, there always appeared a considerable quantity of meta-acetylaminobenzoic acid, that is, a combination of meta-aminobenzoic acid with acetic acid. The acetic acid was supplied by the organism and was coupled with the amino group of the amino-acid with the splitting out of a molecule of water. The reaction is pictured on the preceding page.

After obtaining such results with the meta compound, both the ortho-aminobenzoic acid (anthranilic acid) and the para-aminobenzoic acid were fed to human beings, dogs and rabbits. It was found that the anthranilic acid while quite toxic was not acetylated (i. e., joined with acetic acid) but was excreted unchanged by both the human being and the rabbit. On the contrary, the para-aminobenzoic acid not only proved to be so nontoxic that as much as 5 Gm. could be taken by a human being without causing discomfort, but in addition it was much more completely acetylated by both the human being and the rabbit than the meta-aminobenzoic acid described above.

Certain of these detoxication reactions have at different times been used as organic function tests, one of the best known cases being the hippuric acid synthesis employed by Kingsbury as a renal function test.[9]

Since Knoop and Kertess[10] have shown that the acetylation of phenylaminobutyric acid is brought about by the perfused liver, we thought it worth while to study the acetylation of aminobenzoic acid in the normal human body and compare these results with those obtained after feeding the same compound to persons with some known "liver derangements." For this work we chose the para-aminobenzoic acid as it was both relatively inexpensive and at the same time less toxic than the meta-aminobenzoic acid. Moreover, it seemed to combine in the human body with acetic acid in much larger proportions than the meta compound.

METHOD

The method thus far employed is too cumbersome to be used as a clinical method even should the test prove otherwise satisfactory. We are at present trying to devise a simpler means.

The twenty-four hour urine volume is collected after feeding the subject 5 Gm. of para-aminobenzoic acid and is thoroughly mixed. Then 100 cc. is measured out, exactly neutralized to litmus with an alkali and evaporated to a thick syrup over a water bath. The neutralization prevents the escape of all volatile acids on evaporation. The syrupy residue is cooled, made acid with sulphuric acid to Congo red indicator,

9. Kingsbury, F. B., and Swanson, W. W.: J. Biol. Chem. **46**:4, 1921.
10. Knoop, F., and Kertess, E.: Ztschr. f. physiol. Chem. **71**:252, 1911.

then extracted with ether (preferably in a rotary type extractor) for six hours. As a rule an hour and a half is sufficient to extract all the acetylaminobenzoic acid. This ether extract contains all the acetylaminobenzoic acid, but there is also present with it the uncombined para-aminobenzoic acid to a large extent.

The ether is quickly removed by evaporation or distillation, and the residue, containing the free and acetylated aminobenzoic acid, is then taken up with 100 cc. of 20 per cent sulphuric acid, placed in a distilling apparatus and boiled for half an hour. Into the distilling flask is inserted a dropping funnel through which water is allowed to drop into the distilling flask as fast as it distils out; in this way the contents of the flask are kept equivalent to a 20 per cent solution of sulphuric acid. The distillate is received in a flask containing tenth normal sodium hydroxid. The sulphuric acid coming in contact with the free para-aminobenzoic acid forms the addative sulphate compound which, being soluble and nonvolatile, remains dissolved in the flask and does not distil over. Cold sulphuric acid has no effect on the acetylated aminobenzoic acid but boiling hydrolyzes the compound into acetic acid and para-aminobenzoic acid, the former distilling over while the latter is held in the flask as a sulphuric acid complex.

After the distillation is complete the tenth normal sodium hydroxid solution, into which the acetic acid distillate was received, is titrated with tenth normal acid solution. From the difference in the number of cubic centimeters of tenth normal alkali originally taken and of tenth normal acid required for the back titration the amount of acetic acid in the distillate can be calculated and, consequently, the amount of para-aminobenzoic acid acetylated after the 5 Gm. dose can be determined.

In order to determine the normal acetylation value for a given dose of para-aminobenzoic acid we administered to each of ten normal subjects 5 Gm. of para-aminobenzoic acid. The urine was collected in two portions, the first portion starting immediately after the ingestion of the substance and ending with the expiration of the first twenty-four hours, and the second portion beginning with the twenty-fifth hour and ending with the forty-ninth hour. These samples were treated as follows: One-half the sample was evaporated to a thick syrup and repeatedly extracted with ethyl acetate. The resulting acetylaminobenzoic acid was then recrystallized from hot water and weighed as pure para-acetylaminobenzoic acid. The other half of the sample was worked up according to the clinical method (described above), that is, by determining (in triplicate) the amount of acetic acid formed by hydrolysis of the acetylated aminobenzoic acid.

The acetic acid method (clinical method) gives results that are always somewhat higher than those obtained by the extraction method. Thus,

according to Table 1, the average amount of benzoic acid acetylated during the first twenty-four hours as determined by the extraction method is 66.5 per cent, while according to the clinical method it is 68.5 per cent. The amount detoxicated during the second twenty-four hours is quite variable according to the extraction method, while the quantities present are too small to be determined accurately by the clinical method. This difference between the results of the two methods can be accounted for in two ways. First, there is always a slight loss in extracting and recrystallizing the para-acetylaminobenzoic acid. Second, there is always a small amount of hippuric acid present in a twenty-four hour sample of urine which on hydrolysis with a mineral acid breaks up into glycocoll and benzoic acid. The latter, being volatile, thus augments the total acidity in the distillate and is counted as acetic acid.

In the clinical work the average amount of a 5 Gm. dose of para-aminobenzoic acid acetylated during the first twenty-four hours by a normal human being, namely, 68.5 per cent as determined by the clinical method, was taken as 100 per cent efficiency. Thus, for example, if in a pathologic case 50 per cent is acetylated instead of the normal amount of 68 per cent, then $50/68 = 73.5$ per cent, that is, the efficiency as measured by the ability to detoxicate para-aminobenzoic acid by acetylation is 73.5 per cent normal.

Through the courtesy of Dr. Lewis K. Neff, the test was applied to patients in the medical wards of the Harlem Hospital. The cases chosen were those that exhibited probable liver damage and included carcinoma of the liver, cholecystitis, cirrhosis hepatitis (toxic) due to arsphenamine, catarrhal jaundice, abscess of the liver, and carcinoma of the head of the pancreas. Four patients were operated on and in two others necropsy was performed. In several, the phenoltetrachlorphthalein liver function test of Rosenthal was used, and also icteric indexes measured with the 1:10,000 potassium dichromate standard. The technic of administering the para-aminobenzoic acid together with the method of carrying out the test was the same as that described in the discussion of the normal cases. The results are given in Tables 1 and 2.

COMMENT AND SUMMARY

In this short series of cases the degree of liver function efficiency as determined by the acetylation of para-aminobenzoic acid coincided with the approximate estimation of the same as judged from the clinical picture. In Cases 1 and 4, Table 1, in which no acetylation had taken place, necropsy revealed a most extensive involvement of the liver by carcinoma. Patient 10, Table 1, had a moderately large solitary liver abscess which was sterile and which failed to show amebas on repeated

warm stage examination. This patient had a 60 per cent test, was operated on and had an uneventful recovery. Patient 9, Table 1, was suffering from a severe grade of chronic nephritis and at the time of the test was in a preuremic state. Nevertheless this patient was able to

TABLE 1.—*Pathologic Subjects*

Subject	Date	Weight, Pounds	Age	Diagnosis	Normal* Acetylation, per Cent	Remarks
1	6/ 6/24	110 (49.9 kg.)	58	Metastatic carcinoma of liver	0	Necropsy: extensive carcinoma of liver
2	6/ 5/24	150 (68 kg.)	59	Cirrhosis of liver.....	40	Discharged at own request
3	5/15/24	160 (72.6 kg.)	53	Cholecystitis.....	70	Operation: chronic cholecystitis
4	8/22/24	100 (45.4 kg.)	48	Carcinoma of liver....	0	Operation: extensive carcinoma of liver
5	9/20/24	187 (84.8 kg.)	56	Carcinoma of head of pancreas	75	Phenoltetrachlorphthalein test 25 per cent in 1 hour; icterus index 125
6	9/20/24	160 (72.6 kg.)	26	Cholecystitis.....	86	Operation: negative findings; complete recovery
7	10/ 1/24	130 (59 kg.)	69	Catarrhal jaundice....	83	Phenoltetrachlorphthalein test 3 per cent in 1 hour; complete recovery clinically
8	9/26/24	118 (53.5 kg.)	49	Cerebrospinal syphilis with possible arsphenamine intoxication	84	Faint icterus; cleared up rapidly
9	11/17/24	110 (49.9 kg.)	62	Chronic nephritis.....	93	Preuremia; marked retention of blood metabolites; died 6 days after test
10	1/ 8/25	130 (59 kg.)	29	Abscess.....	60	Operation followed by recovery
11	6/ 9/25	155 (70.3 kg.)	62	Cardiac renal disease..	91	Cardiac decompensation with general anasarca

* By normal acetylation (i. e., 100 per cent) is meant the 68.5 per cent of ingested acid acetylated by a normal subject.

TABLE 2.—*Normal Subjects*

Subject	Sex*	Age, Years	Weight, Pounds	Weight, Kg.	Acetylaminobenzoic Acid Isolated: First 24 Hour Urine, Gm.	Acetylaminobenzoic Acid Isolated: Second 24 Hour Urine, Gm.	Acetylated: First 24 Hours, per Cent	Acetylated: Second 24 Hours, per Cent	Acetylated According to Clinical Method: Per Cent	Acetylated According to Clinical Method: Average
1	♂	38	137	62.1	4.29	1.21	64	18	66, 66, 68	67
2	♂	21	147	66.7	4.18	1.01	64	15	69, 67, 68	68
3	♂	19	129	58.5	4.55	0.0	69	..	70, 69, 71	70
4	♀	29	132	59.9	4.40	0.39	67	6	69, 69, 64	67
5	♂	20	140	63.5	4.66	0.97	71	15	70, 71, 71	71
6	♂	32	178	80.7	4.22	0.13	64	2	67, 69, 70	69
7	♂	22	156	70.8	4.41	1.12	67	17	71, 68, 68	69
8	♀	23	112	50.8	4.48	0.67	68	10	70, 70, 71	70
9	♂	21	142	64.4	4.40	0.18	67	3	72, 68, 67	68
10	♂	19	137	62.1	4.16	0.74	64	11	67, 65, 65	66

Each subject ingested 5 Gm. of para-aminobenzoic acid as a solution of the sodium salt.
* In this column, ♂ indicates male; ♀, female.

acetylate between 90 and 93 per cent of the normal amount. She died only six days later. This would seem to indicate that severe nephritis does not interfere with the estimation of liver function by this test. Patient 11, Table 1, had chronic nephritis with marked cardiac changes and cardiac decomposition, showing general anasarca, large liver and ascites. This

patient also returned a practically normal reading (91 per cent). Here we were dealing with the enlarged liver of chronic passive congestion in which condition the liver apparently functions well. This has been our result with the dye test also. The case of cirrhosis, in giving a 40 per cent normal acetylation value, indicated moderately severe damage to the liver. Catarrhal jaundice and chronic mild cholecystitis gave results only slightly short of normal. These cases were quite mild from clinical signs, symptoms and the lack of intoxication.

These results indicate in general that severe liver damage gives low readings (zero with the two carcinoma cases); that mild liver involvement (clinically) gives only slightly lowered readings, as in Cases 3, 6 and 7, while diseases of other organs though severe do not give lowered readings, as in Cases 9 and 11.

The threshhold at which a subnormal reading first occurs, or the amount of liver tissue which has to be destroyed before changes in the test take place, is being studied at present.

Though the paucity of cases in this preliminary paper does not warrant the drawing of any sweeping conclusions regarding the ability and the accuracy of this test for measuring liver function impairment, and still less for detecting small deficiencies, however we may safely say:

1. The acetylation of para-aminobenzoic acid takes place in the liver (Neuberg).

2. The reaction offers an index of liver function.

3. The test is probably not interfered with by severe cardiac or renal diseases.

4. Clinically the test is easily performed.

5. At present, however, the quantitative chemical estimation of the acetylated para-aminobenzoic acid in the urine is cumbersome.

PAROXYSMAL DYSPNEA AS A SYMPTOM OF SYPHILITIC AORTITIS *

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Paroxysmal dyspnea is so common a manifestation of aortic insufficiency dependent on syphilitic aortitis, often, indeed, being the first symptom of this disease, that it has been generally accepted that it is due directly to the presence of syphilitic aortitis, particularly when the lesion is situated at the root of the aorta.[1] This view is apparently strengthened by the fact that paroxysmal dyspnea is practically never associated with aortic insufficiency of rheumatic origin.[2] Our own experience in this hospital has certainly been in agreement with that of the writers to whom reference is made. From about thirty to fifty cases of aortic insufficiency developing on the basis of syphilis of the aorta are seen every year, ad nin almost all these a history of attacks of paroxysmal dyspnea can be elicited on careful questioning, substantiated usually by actual observation of the attacks in the wards.[3]

We have come to feel a certain amount of doubt, however, whether paroxysmal dyspnea is dependent directly on syphilitic lesions of the aorta. When one attempts to examine many of the earlier descriptions of syphilitic aortitis, such as the ones of Huchard [4] and of Dieulafoy,[5] one finds no statement as to whether the cases showing paroxysmal dyspnea had only syphilitic aortitis, or whether they were complicated by the presence of other lesions, such as aortic insufficiency. Of the nine cases reported by Longcope [6] in which paroxysmal dyspnea was present, all were associated with aortic insufficiency. In Lamb's [7] series

* From the medical clinic of Johns Hopkins Hospital and University.

1. Huchard, H.: Traité clinique des Maladies du Cœur et de l'Aorte, Paris, Gaston Doin **2**:298, 1899. Dieulafoy, G.: Manuel de Pathologie Interne, Ed. 3, Paris, Masson & Cie, **1**:834, 1901. Longcope, W. T.: Syphilitic Aortitis: Its Diagnosis and Treatment, Arch. Int. Med. **11**:15 (Jan.) 1913. Lamb, A. R.: Syphilitic Aortitis and Aneurysm of the Aorta, Nelson Loose-Leaf Living Medicine **4**:531, 1924. Vaquez, H.: Diseases of the Heart, Trans. by G. F. Laidlaw, Philadelphia, W. B. Saunders Company, 1924, p. 382.

2. Coombs, C. F.: Rheumatic Heart Disease, New York, William Wood & Co., 1924, p. 142

3. We have occasionally seen paroxysmal dyspnea in patients with myocardial disease (without hypertension or valvular defects) due either to syphilis or to arteriosclerosis. They do not happen to be included in the group of cases we have studied.

4. Huchard (Footnote 1, first reference).

5. Dieulafoy (Footnote 1, second reference).

6. Longcope (Footnote 1, third reference).

7. Lamb (Footnote 1, fourth reference).

of twenty-six cases, in which the clinical diagnosis of simple aortitis was made, that is to say, none had aortic insufficiency or aneurysm; eight cases showed attacks of paroxysmal dyspnea. Five of the entire group had chronic nephritis, apparently with hypertension, and several of the others had either high systolic blood pressures (150 mm. of mercury or over) or high diastolic blood pressures (90 mm. of mercury or over). It is not stated whether the patients with paroxysmal dyspnea fell into the group with hypertension, and, as we shall see later, it is a matter of considerable importance to the subject under discussion. Hubert [8] states that in 118 cases of uncomplicated aortitis outspoken cardiac asthma was present in none.

We have attempted to gather some information concerning this question by analysis of our own cases. We have first of all taken from the necropsy records a number of cases that showed definitely the anatomic lesions of syphilitic aortitis. From both the clinical and the pathologic data of these cases, we have ascertained the presence or absence of certain other conditions: aortic insufficiency, myocardial involvement due to other causes, myocardial insufficiency, aneurysm and hypertension (with or without renal involvement). From the clinical records, we have determined whether paroxysmal dyspnea or dyspnea on exertion was present. There was no selection of cases except that we have discarded those in which the data that we sought were not absolutely clear, and we also have omitted cases in which the syphilitic lesions of the aorta were not situated in their characteristic location, namely, at or near the root of the aorta. We wish to emphasize the fact that the cases we have used for study have been ones in which syphilitic aortitis has been definitely proved to be present at necropsy.

The results of our investigation are given in the accompanying table.

Analysis of Eighty-Two Cases of Syphilitic Aortitis with Especial Reference to Presence of Dyspnea

Type of Lesion	Total Number of Cases	Cases Showing Dyspnea on Exertion	Cases Showing Paroxysmal Dyspnea	Cases with Myocardial Insufficiency
Uncomplicated syphilitic aortitis	24	0	0	0
Syphilitic aortitis with aortic insufficiency	28	27	25	26
Syphilitic aortitis with aortic insufficiency and aneurysm of root or arch of aorta	5	5	5	5
Syphilitic aortitis with aneurysm of root or arch of aorta	12	6	4	4
Syphilitic aortitis with hypertension	10	10	5	10
Syphilitic aortitis with extensive scarring of myocardium	2	2	0	2
Syphilitic aortitis with laryngeal obstruction due to tumor	1	0	1	0

8. Hubert, G.: Zur Klinik und Behandlung der Aortensyphilis, Deutsch. Arch. f. klin. Med. **128**:317 (Feb.) 1919.

COMMENT

The table needs but little comment. In none of the cases of uncomplicated syphilitic aortitis, twenty-four in number, was paroxysmal dyspnea present. This symptom occurred in almost all the cases associated with aortic insufficiency, and in a number of those with hypertension. It was also present in a fair proportion of the cases of aneurysm of the root or arch of the aorta without aortic insufficiency. Since it seems apparent, at least from the cases that we have studied, that syphilitic aortitis in itself fails to bring on paroxysmal dyspnea, it is likely that aneurysms in this location produce paroxysmal dyspnea by mechanical compression of the trachea or possibly of the recurrent laryngeal nerve, or because they are associated with myocardial damage of one sort or another. If we except aneurysms, then, the chief conditions that have paroxysmal dyspnea as one of their outstanding symptoms are aortic insufficiency due to syphilitic aortitis and hypertension.[9] The question arises as to why cases of aortic insufficiency due to syphilis show this symptom and why cases of aortic insufficiency of rheumatic origin do not. It is not altogether surprising, however, that these two conditions should differ clinically, since they differ in other respects, anatomically and in their natural history. On the other hand, aortic insufficiency of syphilitic origin has much in common with hypertension. In both these conditions, one sees anatomically the huge hearts characterized mainly by hypertrophy and dilatation of the left ventricle. We recognize that myocardial insufficiency is a state of functional impairment in which the whole myocardium participates, yet it seems true that in these two conditions, aortic insufficiency due to syphilitic aortitis, and hypertension, it is the left ventricle that seems to bear the brunt of the burden. Clinically, they are the conditions in which Cheyne-Stokes respiration is encountered most frequently, and also those in which sudden attacks of pulmonary edema are most likely to develop; when myocardial failure supervenes, the course is generally rapidly downhill. Why paroxysmal dyspnea should be so frequent a symptom of these two diseases is not clear, since the fundamental cause of paroxysmal dyspnea is not definitely understood. The recent work of Eppinger and his associates [10] is of interest in this connection. They have presented evidence to show that during attacks of cardiac asthma (paroxysmal dyspnea) there is a striking increase in the circulatory minute volume. They explain the development of paroxysmal dyspnea

9. By hypertension we shall mean either chronic nephritis with hypertension or the condition known as essential hypertension.

10. Eppinger, H.; von Papp, L., and Schwarz, H.: Ueber das Asthma Cardiale, Versuch zu einer peripheren Kreislaufpathologie, Berlin, Julius Springer, 1924.

and pulmonary edema on the assumption that the left ventricle becomes unable to cope with the increased volume of blood brought to it.

All the patients with paroxysmal dyspnea (excepting those with tracheal obstruction) have had as a symptom, besides dyspnea on exertion, other gross evidences of myocardial failure. Apparently there are some cases, such as those described by Longcope,[6] in which paroxysmal dyspnea may develop for months before the usual signs of myocardial failure appear. It does not follow, however, that this symptom may not be a manifestation of myocardial insufficiency, as Longcope has intimated. It is not unusual to see patients suffer from dyspnea on exertion for a long time before gross signs of myocardial failure appear, and in these cases it is generally accepted that dyspnea on exertion is due to myocardial insufficiency.

Our purpose is to point out that, so far as one may judge from a study such as we have made, paroxysmal dyspnea is not a manifestation of uncomplicated syphilitic aortitis. When this symptom is seen in such cases, it is usually due to the presence of aortic insufficiency. We do not mean to imply thereby that paroxysmal dyspnea loses all its diagnostic significance. Undoubtedly, the presence of this striking symptom points definitely to the syphilitic origin of a case of aortic insufficiency, the cause of which might otherwise be obscure.[11] But this symptom indicates the presence of syphilitic aortitis not because syphilitic aortitis is directly responsible for the occurrence of paroxysmal dyspnea, but because it leads to the development of a peculiar kind of heart disease. A condition somewhat analogous is carcinoma of the pylorus of the stomach. The symptoms caused by this lesion, though usually characteristic, are dependent in the main on the location of the growth, rather than on the growth itself.

SUMMARY

In eighty-two cases of syphilitic aortitis proved by necropsy to have the characteristic anatomic lesions, paroxysmal dyspnea was present only when associated with aortic insufficiency, hypertension or aneurysm of the root or arch of the aorta. It would seem, therefore, that paroxysmal dyspnea was not a symptom due directly to syphilitic aortitis. Nevertheless, it is an important symptom in the differentiation between aortic insufficiency of syphilitic and of rheumatic origin.

11. There are rare cases of cardiovascular hypertensive disease that lead to the development of aortic insufficiency without any other demonstrable cause being discovered. That is to say, there may be insignificant atherosclerotic changes in the aorta, and there may be no evidence of syphilitic involvement of the aorta, or of rheumatic heart disease. In these patients, paroxysmal dyspnea may occur, and we do not know of any means by which this type of case may be differentiated from those of aortic insufficiency dependent on syphilitic aortitis, associated with cardiovascular hypertensive disease, except by the blood Wassermann reaction.

EVIDENCE OF NERVOUS CONTROL OF LEUKOCYTIC ACTIVITY BY THE INVOLUNTARY NERVOUS SYSTEM *

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The leukocytes, their various activities, their independent life in the circulating blood, and their importance in the human economy have been a subject of medical research ever since the discovery of their existence.

Though leukocytes play an important part in all local processes connected with infection and inflammation, they are produced in only one organic system, namely, in the bone marrow of the short bones (vertebrae, ribs, skull) and in the short bones of the hands and feet. In times of great need, as for instance during acute general infections, such as pneumonia, leukocytes are also formed in the long bones of the extremities, which usually contain only fatty tissue. In studying leukocytosis and the activity of individual leukocytes and especially the cause of the appearance of large numbers of leukocytes of the polymorphonuclear type in such infected areas, an interesting problem presented itself. As far as human beings are concerned the well known old theory of chemotaxis, first established by the botanist Pfeffer, is unsatisfactory. It may be that in test tubes as well as under the abnormal conditions surrounding experimental work in animals, leukocytes will accumulate around germs, moved by chemotactic processes, but even so the question of the cause of leukocytic migration is not settled as long as the vessels are not injured, as is prerequisite to animal experimentation.

Before a description of the details of our studies is given, the problem itself should be made as clear as possible. In using the word migration we do not mean the passage of leukocytes from the vessels through their walls into the tissues but rather their movement in the normal circulation to a given point in the circulatory system. For instance, we know that in gonorrhea not involving a general leukocytosis, the already existing leukocytes gather in the vessels of the inflamed part and that these leukocytes later appear in the excretions. The same migration of leukocytes to areas of inflammation is known to take place in cases of metastatic foci (septicemia); but our problem deals only with the power that impels the leukocytes to migrate from their site of production through the circulation to an infected area and which then

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* Read before the Chicago Pathologic Society, Feb. 9, 1925.

for a time keeps them from the circulation, confined at the site of inflammation.

Research in human beings along these lines became possible when it was recognized that a reaction of the leukocytes consists of a sudden displacement of large numbers of these organisms from one part of the body to another.

From experiments first carried out by Goldscheider and Jacob [1] it is well known that a drop in the number of leukocytes in the peripheric vessels follows immediately on injection of peptone solution into the circulation. Recent experiments along these lines revealed that almost no leukocytes are present in the peripheral blood, for perhaps ten minutes after the injection of 10 c.c. of a 20 per cent. peptone solution and that these leukocytes accumulate in the vessels that are controlled by the splanchnic nerve, particularly those in the liver.[2] Although usually a slight increase of leukocytes in the periphery follows the ingestion of food, certain patients will show a slight drop after drinking milk on an empty stomach. This phenomenon, first observed by Widal [3] has been termed "crise hemoclasique." Experiments have shown that during the slight decrease of the Widal test, which was reproduced in animals, and also during the period of the decrease of the leukocyte count in the peripheral vessels, the leukocytes accumulate in the splanchnic region. The last discovery along these lines has been that injections of non-specific albumin preparations, as well as of minute amounts of salt solution, of distilled water and even of air, are capable of producing an immediate leukopenia in the entire periphery.[4] This leukopenia lasts for perhaps thirty minutes if produced by albumin injections and for from five to ten minutes if caused by the introduction of air or physiologic sodium chlorid solution into the skin.

The discovery that acute leukopenia follows the injection of albumin in every human being, normal or diseased, with the exception only of persons afflicted with certain skin diseases, makes it possible to study the reasons for this leukocytic displacement and points the way to ascertaining the cause of leukocytic activity.

It is astonishing, indeed, that the intradermal injection of a nonirritating albumin that does not cause the slightest pathologic change in the cells and tissues surrounding the site of injection should cause a reaction in the entire circulation. This phenomenon consists not only of a local change of the leukocytes in the vessels involved by the injec-

1. Goldscheider, A., and Jacob, P.: Ztschr. f. klin. Med. **25**:373, 1894.
2. Mueller, E. F., and Myers, C. N.: Proc. Soc. Exper. Biol. & Med. **22**:95, 1924.
3. Widal, F.; Abrami, P., and Brissaud, E.: Presse méd. **28**:181 (April 3) 1920.
4. Mueller, E. F.: München. med. Wchnschr. **69**:1506-1753 (Oct. 27) 1922.

tion but of a rearrangement of these cells in the entire circulation. Expressed in numbers, the exact loss of leukocytes to the peripheral circulation and their accumulation in the vessels controlled by the splanchnic nerve reaches from 50 to 75 million; these leukocytes are actually moved from one place to another. In discussing such a migration it must be taken into account that leukocytes are not stationary in the body, but rather that they are continually in circulation and that, normally, they are evenly distributed, an equal number of cells being found in equal amounts of fluid serum. It has been proved experimentally that within a period of one hour the total number of leukocytes does not vary so long as the individual keeps quiet and experiences no physical or mental excitement.

The intradermal injection of a mild preparation acts in the manner described. No more than 0.2 c.c. of a solution containing about 4 per cent. of albumin is given intradermally; in actual numbers 0.0012 gm. of albumin is introduced into the skin where it remains unabsorbed as a deposit during a period of about ten minutes. If the same amount of albumin in the same quantity of fluid is given subcutaneously, intramuscularly or intravenously, no change in leukocytes takes place. Tissue excised shortly after any of the latter modes of injection shows no pathologic involvement, nor does the number of leukocytes vary after the injection. But if, on the other hand, not more than two or three drops of the milk preparation are injected into one or two wheals *within the skin* the leukocyte curve will show the drop mentioned in the foregoing. Expressed in percentage this decrease is not influenced by any leukocytosis or by conditions such as leukemia or chronic leukopenia. In normal subjects the number of leukocytes in the peripheric vessels drops from about 8,000 to 5,000; in cases with leukocytosis (as for instance, in pneumonia and in purulent diseases) a drop from 25,000 to 16,000 is observed. Cases of leukemia are reported and I have seen them when the leukocytes have dropped from 150,000, usually observed in such cases, to 70,000 and 80,000, thus showing that the ratio of the decrease remains approximately the same. The actual numbers of the leukocyte drop in the peripheric vessels in cases of leukemia may be given at from about 100 to 120 million. Cases of leukopenia (as for instance, in pernicious anemia) react to intradermal injections of protein with a decrease from about 5,000 to 1,600.

The amount of fluid injected or its solid content, beyond doubt, is unable to produce of itself any organic change in the body. This is proved by the injection of identical substances in equal amounts into other body tissues. Further proof is seen in the fact that the injection into the derma of air instead of the milk preparation and the application of a new kind of very soft roentgen rays, which latter test I have recently

carried out in collaboration with Bucky,[5] exerts an influence on the skin similar to the stimulation by means of intradermal injections of non-specific albumin. The drop in the leukocyte curve produced by the injection of air and the administration of this radiating energy is

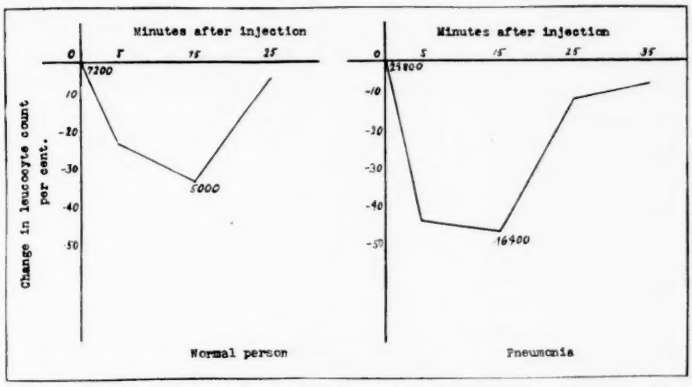

Chart 1.—Peripheral leukopenia after intracutaneous protein injections in normal and in pneumonic patient.

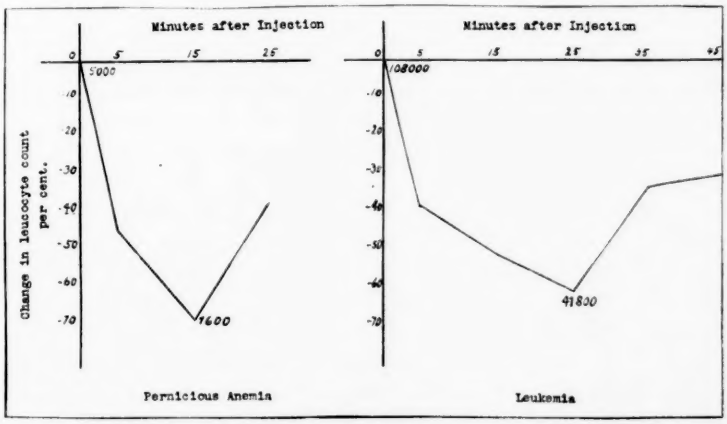

Chart 2.—Peripheral leukopenia after intracutaneous protein injection in pernicious anemia in leukemia.

smaller and does not last as long, nor does it produce certain focal reactions resulting from intradermal injections of the milk preparation. But a comparison with injections into other tissues and the injection of

5. Bucky, Gustav; and Mueller, E. F.: München. med. Wchnschr. **72**:883 (May) 1925.

air into the derma gives evidence that the injected fluid is not the direct cause of the phenomenon but rather the tissues into which the injection is made.

Studies undertaken in the last three years have shown that a close relationship between the skin and the involuntary nervous system, more particularly its parasympathetic part, is responsible for the decrease of leukocytes in the peripheric vessels and for their aggregation in the splanchnic region. By blocking the nerves which carry parasympathetic stimuli to the splanchnic region, i. e., the vasodilators, we were able to demonstrate that it was no longer possible to produce the described changes in the leukocyte curve.[6] Experiments in human beings have shown that epinephrin and atropin, administered in small doses subdermally, in any part of the body, make it impossible, for perhaps half an hour, to influence the leukocyte count by means of intradermal injections. Our studies show that epinephrin, by increasing the tonus of the sympathetic system, acts precisely the same as atropin, decreasing or paralyzing the tonus of the parasympathetic system. Pilocarpin, which acts on the involuntary nervous system by increasing the action of the parasympathetic, does not change the influence of intradermal injections on the leukocytes. On the contrary, pilocarpin as a rule produces a slight drop in the leukocyte curve, so that if, ten minutes after the administration of pilocarpin, a milk preparation is given intradermally, even though the leukocyte count be comparatively low (from 4,000 to 5,000), the intradermal injection causes a still greater decrease to from 2,000 to 3,000, thus proving that the pathways of intradermal stimulation are not disturbed or blocked by pilocarpin.

The decrease of leukocytes following intradermal injections, which actually involves a leukocyte drop in the entire periphery (blood of veins and arteries shows the same decrease observed in the peripheric vessels) and an accumulation of these missing leukocytes in the splanchnic region, is to be based on a sudden change in the vascular system of the splanchnic region produced by parasympathetic stimuli that originate automatically in the human economy after the described skin stimulation.

Thus, it was recognized that the liver and probably also the other blood vessels of the splanchnic region, by means of the described stimuli, accumulate and retain the circulating leukocytes during the period of stimulation. The cause of the leukocytes lodging in these vessels, parasympathetically dilated, is entirely unknown. We can only assume that some chemical or electric relationship exists between the wall of a parasympathetically stimulated and dilated vessel and the fluid and the cells circulating in these vessels. The observation of this migration of leuko-

6. Mueller, E. F., and Hoelscher, R.: Ztschr. f. d. ges. exper. Med. **38**: 478, 1923; **61**:325, 1924.

cytes into the splanchnic region and their retention in the same has been confirmed by animal experiments. The existence of a close relationship between the vessels and the circulating fluid may be concluded from the following tests: If tertiary syphilitic patients with a negative Wassermann reaction are given an intradermal injection of a milk preparation, their serologic reaction will turn positive for two or three days. This experiment, repeated several times, always gave the same result, thus demonstrating that changes in the vascular system are able to influence the colloidal condition of the serum. We are not sure whether the vessels themselves in their state of dilation are able to produce this change in the colloidal condition of the serum, or whether both the vascular and the serologic changes are attributable to some other common cause. Recent studies by Embden and Freundlich [7] on the nature of the phenomenon of sudden peripheric leukopenia have added to our knowledge of its origin.

In patients in whom a so-called sympathectomy has been performed, the intradermal injection of a milk preparation into the derma of such an extremity no longer results in a decrease of leukocytes. The term sympathectomy is incorrect. The actual operation consists in severing the nerves accompanying the large vessels or in excising a ganglion. If the nerves accompanying the main vessels of the extremities were entirely cut off, we would not then state that a sympathectomy had been performed, yet every fiber of the vasoconstrictors and of the vasodilators has been thus disconnected.

It does not pertain to the theme of this paper to go into details about the vascular control of an extremity in which the large fibers of the involuntary nervous system have been cut off, but it may be mentioned that the local control of the peripheric vessels is still in effect, even though the balance is visibly disturbed. But, as stated before, intradermal injections into any part of the skin of such an extremity no longer cause a leukocyte fall.

Thus, it is shown that, after the intradermal injection, the large fibers of the involuntary nervous system play an important part in conducting the stimulus originated in the skin to the vessels of the splanchnic region.

The following discovery, also described by Embden and Freundlich in a confirmation of our previous statements, is of great interest: If, after operative disconnection of the nerves accompanying the large vessels of an extremity, the subject is given an intradermal injection into any part of his body, outside of this extremity, then the leukocyte drop will occur in all the peripheric vessels with the surprising exception of the extremity in which the nerves have been severed. This reveals that

7. Embden and Freundlich, H.: München. med. Wchnschr., to be published.

the splanchnic region is not the only factor active in originating the described phenomenon of the leukocyte curve. If it were merely the task of the splanchnic region to retain the leukocytes, there would be no reason why leukocytes which without difficulty enter and leave that particular extremity should not turn into the splanchnic vessels. If, after the severing of the nerves in one extremity, this particular extremity no longer participates in the phenomenon, then, clearly the part played by this extremity has not been merely a passive one. An active participation in the reaction must have taken place which becomes impossible on disconnection of nerve conductivity. We may therefore conclude that during the period of actual peripheric leukopenia following intradermal injection, both the skin and the splanchnic region share in the production of the phenomenon. The action of the skin must account for the hitherto unexplained influence of the skin vessels themselves on the leukocytes. This influence must be the reverse of the influence of the splanchnic vessels during the leukocyte fall. The splanchnic vessels would seem to attract and the skin vessels to repel the leukocytes, thus influencing their numerical presence. We do not wish to discuss any theoretic possibilities as to how this influence acts; we merely report actual observations. We know that the splanchnic region receives parasympathetic stimuli; the vessels are dilated to a certain degree. The resulting change of the walls and their permeability is somehow related to this dilatation. The leukocytes accumulate, and this accumulation is based on changes in the parasympathetic overbalance of the vessels controlled by the splanchnic nerve, this being evident from the fact that the accumulation lasts only for the period of this parasympathetic overbalance.

The action of the skin vessels is just the reverse as far as the leukocytes are concerned. It was observed that a decrease of the actual number of leukocytes no longer obtains if the nerves are severed and the assumption is warranted that the balance of these vessels is disturbed.

To further study the action of the skin vessels during the leukocyte decrease the following tests were performed: Friction or heat was applied to a part of the skin until the area appeared red; examination revealed that the number of leukocytes had increased 30 per cent. in this artificially congested area. This observation is readily explained: both friction and heat produce dilatation, the immediate cause of which is a reaction of the vasodilator, resembling the reaction of the vessels of the splanchnic region to parasympathetic stimuli. The effect of dilatation on the leukocytes is the same in every region of the body: they accumulate progressively. This simple experiment gives evidence, especially in connection with the phenomenon described above, that vasodilatation by active nerve action causes a local aggregation of leukocytes.

Another simple experiment was carried out: If small amounts of very dilute solutions of epinephrin (1:100,000) are injected subdermally or intradermally, the vessels in the adjoining region show a low leukocyte count that differs from 30 to 40 per cent. from that obtaining in other regions of the body. These experiments must be made carefully. If too much epinephrin is given the vessels will be closed and neither leukocytes nor erythrocytes will be found. However, with the correct concentration—and this varies in different individuals—the surprising fact develops that the leukocytes show a decrease and that this decrease affects only the polymorphonuclear type. The same decrease of leukocytes will be noticed if cold is applied to the skin. A decrease of polymorphonuclear leukocytes will be evident in the affected area, while erythrocytes and lymphocytes remain unchanged. We wish to call attention to the fact that every decrease of leukocytes referred to in this article affects only the polymorphonuclear type, while in from 70 to 80 per cent. of the cases examined, the lymphocytes are not influenced and their numbers not affected. Considering only the proportional figures, the lymphocytes may seem to have increased, but by calculating the absolute value, the lymphocyte curve and the curve of the red cells will be a straight line while the leukocyte curves show a marked dip.

The following conclusions are drawn: If the normal balance of the vasodilating and vasoconstricting nerves is disturbed the number of leukocytes actually present will be found to vary in direct ratio to the overbalance. If the disturbance of the balance of the vasoconstricting nerves is deflected to a sympathetic overbalance, a local leukopenia will immediately result. If the deflection is toward the parasympathetic, and the normal condition of a particular vascular region is overruled by the vasodilating nerves, an immediate leukocytosis will manifest itself and will last as long as this particular disturbance of the vasodilating nerves is effective. This rule, which applies to every region of the body, may be established as an indicator of the balance of the vasocontrolling nerves, and it may lead to evidence of a nervous control of leukocytic activity of which the leukocyte fall is only one feature. It is definitely established that during the time of the phenomenon the entire skin shows an overbalance of the sympathetic nerves over the parasympathetic. Moreover, we know that the liver and the vessels of the splanchnic region show a contrary fixation when the parasympathetic, vasodilating nerves prevail. If that is the case, the splanchnic region, as represented in one part by the liver, and the periphery, as represented in one part by the skin, forms two large systems, balancing each other as far as the nervous control is concerned and holding in balance also the number of leukocytes in their vessels. Furthermore, the skin as a part of the periphery and the liver as a part of the splanchnic region together form

one great entity that is probably controlled by one and the same nervous action.

The last assumption is still unproved. From the mentioned observation we merely know that while the splanchnic region receives parasympathetic stimuli and acts in a parasympathetic overbalance, the skin simultaneously receives sympathetic stimuli and acts in this direction. If periphery and splanchnic region regulate each other and are actually controlled by one mutual nervous action, a reversion of these two stages in both regions must be possible. We have succeeded in demonstrating this reversion.

We shall confine ourselves to a statement of the principal results. If in diabetic patients an abnormally low blood sugar level due to an overdose of insulin is reached, symptoms of so-called insulin shock occur. Insulin shock, as is known, manifests itself as a feeling of weakness, dizziness and trembling of the extremities; then profuse perspiration sets in and the feeling of weakness increases until the patient reaches an alarming condition.

The peripheral symptoms of insulin shock, especially the profuse perspiration of a watery fluid, indicate an overbalance of parasympathetic innervation resulting in dilatation of the vessels and in an increase of endothelial permeability. (This watery perspiration should be clearly distinguished from the perspiration of a more viscid fluid, the product of sympathetically stimulated and functioning sweat glands.) A careful investigation of the number of leukocytes during insulin shock—a condition that has been observed only twice among a large number of diabetic patients treated with insulin—leads to the remarkable discovery that the leukocytes increase with the lowering of the blood sugar. If the blood sugar is lowered beyond a certain limit, for instance, to 50 per cent. of the normal figures, the leukocytes increase rapidly, reaching numbers never observed in fasting patients. In the two cases of insulin shock under observation the leukocytes reached 28,000 and 19,000. In each instance this rise took place within less than fifteen minutes.[8] In both cases the patients had to be given immediate treatment with glucose, to prevent further danger. Then another surprising observation was made: In the very moment in which the patients received their glucose the leukocytes immediately decreased. Glucose was administered by mouth only 5 gm. was given in 100 c.c. of water. In less than ten minutes the leukocytes had decreased to 7,000, the level that obtained prior to insulin treatment.

Simultaneous with the decrease of leukocytes all the alarming symptoms produced by the parasympathetic overbalance in the entire periphery were checked, thus proving complete parallelism between the

8. I observed these cases in the department of metabolism of the Vanderbilt Clinic.

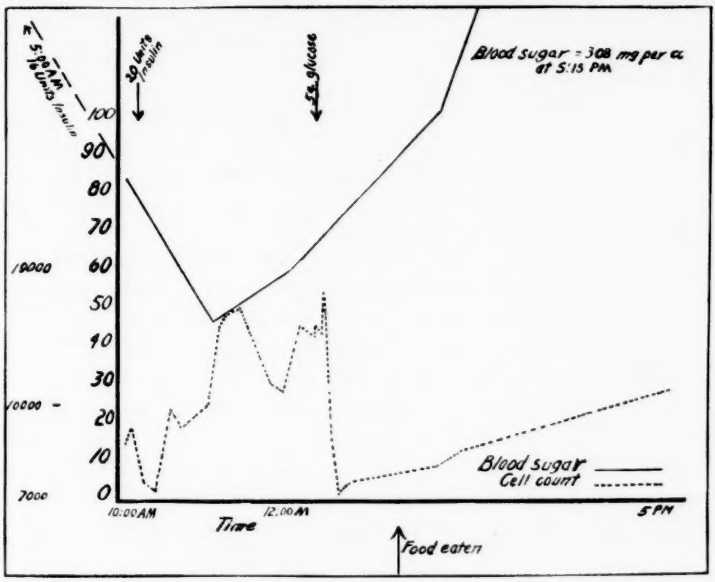

Chart 3.—Relation of leukocyte count to insulin shock.

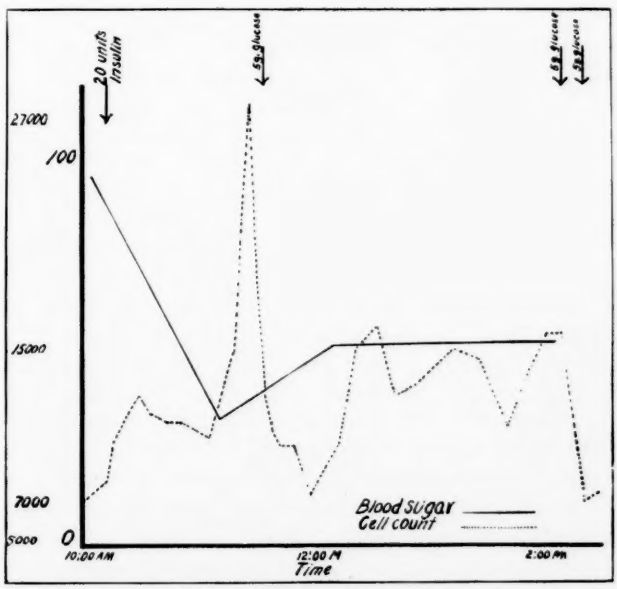

Chart 4.—Relation of leukocyte count to insulin shock.

parasympathetic overbalance in the periphery and the leukocyte curve. That a sympathetic overbalance in the splanchnic region exists at the same time has been shown by more complicated experiments which will be reported later.

As it has not been possible to duplicate in human beings the observations we made accidentally in the two cases quoted, we have performed tests in rabbits, using high doses of insulin and have demonstrated that in 80 per cent. of the rabbits so treated the leukocytes in the ear vein increased markedly (about 20,000), during the time of the low blood sugar level (about 30 per cent.). This phenomenon did not occur uniformly in all rabbits but then these animals are not diabetic, and we know from experience in human beings that insulin shock is unusual in nondiabetic subjects. This observation may offer an explanation of varying results in animal tests. A number of animals, however, showed a distinct parallelism with the findings in human beings, reacting with a decrease of leukocytes to the intraperitoneal injection of glucose which reached the original level in from five to ten minutes.

It is concluded from the foregoing that if the blood sugar is suddenly lowered beyond a certain level, then the skin as a part of the periphery receives parasympathetic stimuli and the result is a dilatation of the vessels, increased permeability, profuse perspiration, increase of leukocytes and the clinical symptoms of insulin shock. The splanchnic region at the same time receives sympathetic stimuli, the nature of which is only partly understood. (The experiments of Claude Bernard have already proved that an abnormal decrease in blood sugar leads to sympathetic stimulation of the liver region the result of which in one particular is to increase the formation of glucose.) These observations practically represent the reversion of the disturbance of balance in the involuntary nervous system which obtains during the period of the so-called leukocyte drop. If in this reversed condition of parasympathetic overbalance in the entire periphery and of sympathetic overbalance in the splanchnic region glucose is given by mouth, the original balance is immediately restored.

The latter observation of the restoration of the balance as affected by a change in blood chemistry, i. e., lowering of the blood sugar, tends to show that nerve action plays a regulating part. If one considers both phenomena, the leukocyte drop and the insulin shock with its peripheric leukocytosis, and if one further considers that the possibility of reversing the disturbance of balance during the leukocyte drop has been demonstrated, the assumption gains in strength that the periphery as represented by the skin and the splanchnic region as represented by the liver are controlled by one nerve center. This nerve center and its anatomic location are unknown. It may consist of one ganglion, it may be a large nervous system; the physiologists will have to locate it. From studies

with the so-called sugar center in the medulla we know that the latter acts in close relation to the center and we furthermore know that a sudden irritation of the solar ganglion produces similar manifestations, as an insulin shock. But this leads us beyond the scope of this article.

A mutual nervous control of the periphery and of the splanchnic region may lead to absolutely new conceptions in some fields of medicine. Other studies along these lines will be published in the near future. Our problem has been to ascertain the cause of leukocytic activity, or more particularly of the migration of leukocytes. Investigation of the leukocyte drop and of its reversion has demonstrated that acute peripheric leukopenia and acute peripheric leukocytosis always correspond to leukocytosis of leukopenia, respectively, in the splanchnic region, depending on the nervous control. Where parasympathetic stimuli predominate in the vascular system, there the leukocytes will accumulate, while an overbalance of sympathetic stimuli produces a decrease of leukocytes in this region. Both processes originate in the involuntary nervous system, the migration of the leukocytes being but a sequel. There is no evidence to support the fact that the leukocytes in their migration are subject to passive transportation only. It is quite possible that the leukocytes actively participate in the described migrations, viz., the accumulation in the periphery or in the splanchnic region. Many theories have been conceived but no facts are established. Whether or not the leukocytes individually take an active part in this migration is not certain. On the other hand, it has been definitely established herewith that leukocytic activity depends on a nerve action. The involuntary nervous system and its branches control the number of leukocytes present at one time in the various regions of the body. Since it is possible by artificial irritation and stimulation of the involuntary nervous system to produce an accumulation of leukocytes in the periphery as well as in the splanchnic region, it is evident that the involuntary nervous system is a dominating factor in the production of this phenomenon. This fact will remain, whether or not new discoveries lead to acceptance of the theory of passive transportation of the leukocytes or of an active response to a stimulus provided by the involuntary nervous system, or of a difference in the electric charge of the leukocytes and walls of the vessels as productive of leukocytic activity. Should the latter possibility, i. e., a difference in the electric charge of the leukocytes and walls of the vessels, obtain, it would only be a sequel to the involuntary stimulus taking effect in that particular vascular region. To future studies may be left the task of developing the new findings and of establishing and completing on the basis of these data entirely new conceptions of focal reaction, inflammation and leukocytic activity in pathologic conditions.

SUMMARY

The number of leukocytes found in any vascular region of the body depends on the balance of the involuntary nervous system in this particular region. The leukocytes will be evenly distributed so long as the involuntary nervous system, vasodilators and vasoconstrictors are in normal balance. The uniform distribution changes immediately if there is an overbalance in either direction. Such an overbalance never takes place in the entire body. If large areas are involved, peripheric and splanchnic regions balance each other. An overbalance of the sympathetic, vasoconstricting portion causes local leukopenia, while overbalance of the parasympathetic, vasodilating part causes leukocytosis. Nervous action is always the primary cause of leukocytic activity as far as accumulation and decrease are concerned, even though the leukocytes are in no way directly connected with either the walls of the vessels or with the vasocontrolling nerves of the involuntary nervous system. This knowledge may furnish a new link connecting immunity and body resistance (of which the leukocytic activity is only one part) with the teachings of pathology and physiology in the human economy.

INTRADERMAL SALT SOLUTION TEST IN CARDIAC DISEASE IN CHILDREN *

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In 1923 McClure and Aldrich [1] reported that when 0.2 c.c. of an 0.8 per cent. aqueous solution of sodium chlorid was injected intradermally in children, the resulting elevation disappeared or became impalpable much sooner in edematous patients than in certain control patients without edema. Shortening of the disappearance time in edematous patients, while most marked in regions of palpable edema, was also found, to a less degree, in areas in which pitting could not be demonstrated. This report included three cases of children with cardiac disease, in each of which the disappearance time was shorter in the leg than in the arm. In a subsequent paper the same authors [2] reported the results of the application of the test in sixteen children having nephritis, with generalized edema. They pointed out that the decreased disappearance time found in remotely separated regions of the body in the same subject could be explained on the assumption that a general intoxication so altered the tissues as to increase their avidity for water. They concluded that the test was of considerable aid in prognosis in this type of case, since a diminution of disappearance time preceded the onset of palpable edema, while an increase of time was a forerunner of its departure.

Baker [3] applied the test to scarlatinal and diphtheric patients and found a decrease in disappearance time, paralleling the severity of the intoxication. Harrison [4] tested children with lobar pneumonia, and determined that the disappearance time was constantly diminished, slowly returning to normal during convalescence; she suggested that this indicates a persistent intoxication of the tissues.

Cohen [5] presented evidence indicating that the intradermal salt solution test may serve as a means of determining the level of adequate

* From the Otho S. A. Sprague Memorial Institute Laboratory of the Children's Memorial Hospital, Chicago.

1. McClure, W. B., and Aldrich, C. A.: Time Required for Disappearance of Intradermally Injected Salt Solution, J. A. M. A. **81**:293-294 (July 28) 1923.
2. Aldrich, C. A., and McClure, W. B.: The Intradermal Salt Solution Test, II, Its Prognostic Value in "Nephritis" with Generalized Edema, J. A. M. A. **82**:1425-1428 (May 3) 1924.
3. Baker, W. J.: Intradermal Salt Solution Test in Scarlet Fever and Diphtheria Patients, J. A. M. A. **83**:1566-1567 (Nov. 15) 1924.
4. Harrison, Jeanette: Intradermal Salt Solution Test in Lobar Pneumonia in Children, J. A. M. A. **84**:1258-1259 (April 25) 1925.
5. Cohen, M. B.: The Intracutaneous Salt Solution Test: Preliminary Report of a Simple Method for Determining the Efficiency of the Circulation in the Extremities, J. A. M. A. **84**:1561-1562 (May 23) 1925.

circulation in local vascular disturbances of the sort that lead to gangrene. He also used the test in two cases of cardiac decompensation in which he found the disappearance time much more decreased in dependent parts of the body than elsewhere.

A survey of the previously demonstrated value of the intradermal salt solution test led to its adoption for the study of cardiac disease in children, particularly with reference to decompensation edema and to prognosis.

CLINICAL MATERIAL

Forty-four children in the cardiac ward and three outpatients, of ages ranging from 4 to 12 years, were included in this study, which extended over a period of ten months. Except for one case of acute ulcerative endocarditis, the diagnosis in all was acute or chronic rheumatic heart disease, or the closely associated conditions of acute rheumatic fever and chorea.

TECHNIC

The standard technic of McClure and Aldrich was used in performing the test. The sites most commonly used were the volar surface of the forearm and the outer or inner posterior aspect of the calf. Two-tenths cubic centimeter of an 0.8 per cent. aqueous solution of sodium chlorid was injected intradermally under aseptic precautions. Two wheals approximately 2 cm. apart were found to be more satisfactory than one in determining the end-point in nonedematous regions, since the "valley" between two elevations was more easily palpated than was a single elevation. The end-point was easily determined in regions of pitting edema. When the disappearance time was normal or nearly so, differences of several minutes were considered within the limit of subjective error.

The tests were made daily or at intervals of a few days or weeks, depending on the severity of the case, and clinical observation of the cardiac condition was noted at the time.

CLASSIFICATION OF CASES

After some experience with the method it became apparent that the cases of cardiac disease fell into four groups with respect to the disappearance time of intradermally injected salt solution. In the first group the time of disappearance was normal over the entire period of weeks or months in which the test was performed; i. e., it remained constantly above fifty minutes in both arm and leg. Figure 1 represents a case of this type.

In the second group (Fig. 2), the disappearance time in the leg was much reduced, while that in the arm remained normal or nearly

so, until the edema ascended to the upper regions. Clinically these patients had pure cardiac decompensation, with edema mainly in the dependent parts of the body.

In the third group (Fig. 3), there was a persistently lowered and nearly equal disappearance time in arm and leg; these patients died without becoming edematous in the manner of ordinary cardiac decompensation. In the fourth group (Fig. 4), the disappearance time curves, in certain periods, resembled those of the third group, becoming modified to approach those of the second group with the advent of cardiac decompensation.

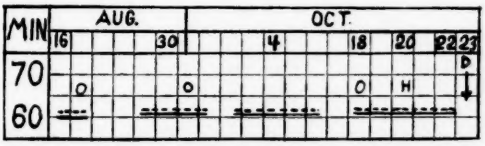

Fig. 1.—Group 1: solid line, disappearance time in arm; broken line, in leg; points above 60, more than sixty minutes; *O*, registered as outpatient; *H*, admission to hospital; *D*, death.

Table 1 shows the distribution of the cases of the four groups according to the chief clinical diagnosis. Each group will be discussed separately.

TABLE 1.—*Classification of the Four Groups of Cases According to Diagnosis*

Group	Acute Endocarditis	Chronic Endocarditis	Acute Pericarditis	Adhesive Pericarditis	Acute Rheumatic Fever	Chorea	Total Number of Cases
1. Normal time.....	0	12	1	2	2	4	21
2. Decompensated..	0	5	3	4	0	0	12
3. Toxic.....	3	2	1	3	0	0	9
4. Combined.....	0	2	1	2	0	0	5

NORMAL DISAPPEARANCE TIME IN CARDIAC AND ALLIED DISEASE

Twenty-one patients showed no lowering of disappearance time. Fifteen of these, from a history of rheumatism or previous cardiac decompensation, and from clinical examination, were determined to have organic heart disease, but were well compensated. Several were up and about in the ward, and three were outpatients attending school. All of the cases of chorea and acute rheumatic fever and one case of acute pericarditis fell in this group having normal disappearance time.

The patient whose disappearance time curves are represented in Figure 1 had chronic rheumatic endocarditis. He was well compensated, attending school, and showed a normal disappearance time, whenever tested, over a period of two months. The patient then devel-

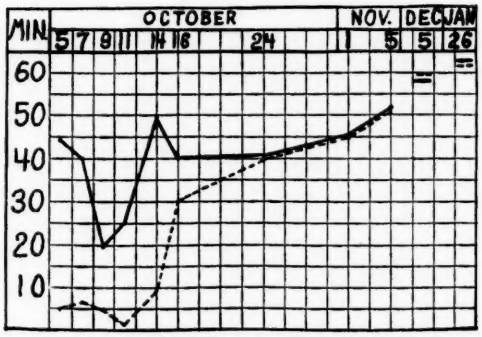

Fig. 2.—Group 2: solid line, disappearance time in arm; broken line, in leg; points above 60, more than sixty minutes.

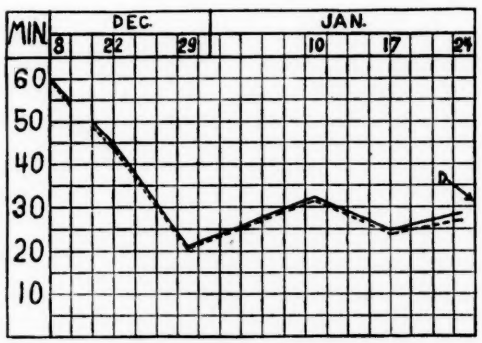

Fig. 3.—Group 3: solid line, disappearance time in arm; broken line, in leg; *D*, death.

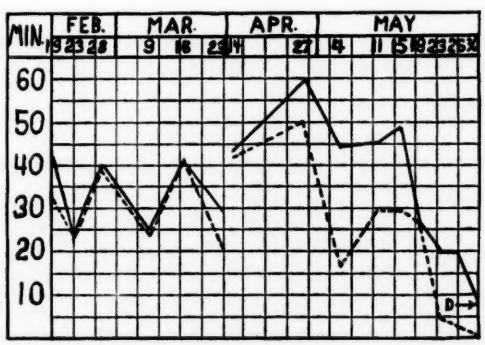

Fig. 4.—Group 4: solid line, disappearance time in arm; broken line, in leg; *D*, death.

oped tachycardia, was admitted to the hospital, and died at the end of three days, probably of myocardial failure, without the advent of clinical evidence of decompensation. Disappearance time remained normal until death.

TABLE 2.—*Cardiac Decompensation*

Case; Age	Date, 1924	Forearm: Palpable Edema	Forearm: Disappearance Time*	Calf: Palpable Edema	Calf: Disappearance Time*	Urine	Clinical Notes
1 6 years	10/ 5	0	44 min.	++	5 min.	Albumin + Casts +	Admitted to hospital; dyspnea; slight cyanosis; large liver; ascites
	10/ 7	0	40 min.	++	7 min.	.....	Left hydrothorax
	10/ 9	+	20 min.	++	5 min.	Albumin + Casts +	Increased dyspnea
	10/11	+	25 min.	++	1½ min.	.....	Decreased ascites
	10/14	0	49 min.	+	8 min.	.....	Decreased dyspnea
	10/16	0	40 min.	+	30 min.	Albumin +	Decreased dyspnea
	10/24	0	39 min.	0	38 min.	.....	Minimal ascites
	11/ 1	0	46 min.	0	45 min.	.....	No ascites or dyspnea
	11/ 5	0	52 min.	0	51 min.	Albumin +	In bed; no dyspnea
	12/ 5	0	56 min.	0	60 min.	.....	
	1925 1/26	0	60 min.+	0	60 min.+	.....	Up part of day
	2/25	0	60 min.+	0	60 min.+	.....	Up and about
	4/ 1	0	51 min.	0	51 min.	.....	Home; clinical diagnosis: chronic endocarditis; mitral stenosis
2 9 years	2/15	0	50 min.	++	18 min.	.....	Dyspnea; cyanosis; enlarged liver; sacral edema
	2/17	0	54 min.	++	23 min.	Albumin +	No dyspnea or cyanosis
	2/19	0	60 min.+	+	28 min.	.....	No edema
	2/23	0	60 min.+	+	33 min.	.....	
	2/28	0	60 min.+	0	50 min.	.....	Bed rest
	3/11	0	60 min.+	0	60 min.+	.....	
	3/30	0	60 min.+	0	42 min.	.....	
	4/14	0	60 min.	0	60 min.+	.....	Up and about
	5/ 4	0	58 min.	0	58 min.	.....	Home; clinical diagnosis: mitral endocarditis and stenosis; adhesive pericarditis?
	1924						
3 11 years	11/ 8	0	57 min.	++	18 min.	Albumin + Casts 0	Admitted to hospital; dyspnea; enlarged liver; edema of feet
	11/13	0	44 min.	++	16 min.	Albumin +	Continued dyspnea
	11/15	+	25 min.	+++	6 min.	.....	Ascites
	11/19	++	20 min.	+++	4 min.	.....	Face puffy; increased ascites
	11/25	Upper Arm 0	24 min.	+++	1 min.	Albumin + Casts +	Face puffy; ascites +++; scrotal edema
		Forearm +++	1 min.	....	.....	.....	
	11/28	Shoulder 0	20 min.	++++	10 sec.	.....	Marked dyspnea and cyanosis; impending heart failure
		Upper Arm ++	45 sec.	....	.....	.....	
		Forearm +++	30 sec.	....	.....	.....	
	11/30	....	.....	....	.....	.....	Died; clinical diagnosis: adhesive pericarditis and chronic endocarditis

*In this and the succeeding tables, 60 min.+ in this column means more than sixty minutes; elsewhere, + means slight; ++, moderate, etc.

DISAPPEARANCE TIME IN CARDIAC DECOMPENSATION

Chronic endocarditis, acute pericarditis and chronic (adhesive) pericarditis were about equally represented in this group of twelve cases in which, at some time during the period of observation, cardiac decompensation with edema was present. Table 2 gives data on three cases of this kind, one of which, Case 1, is represented in Figure 2. While the disappearance time in the edematous legs was markedly reduced from the onset of decompensation edema, the time in the nonedematous arms remained normal or nearly so until edema ascended to the upper parts of the body. In these patients edema of the face never preceded that in the lower regions, and often did not occur even in the presence of an otherwise generalized edema. In Case 3 in Table 2, a striking regional difference in disappearance time is shown; November 25, the time was much less in the dependent, edematous forearm than in the slightly edematous or nonedematous upper arm.

Decrease in disappearance time did not precede other clinical evidence of impending decompensation constantly enough to make the test of value in predicting a break in compensation in cases of this type.

GENERALIZED OR "TOXIC" TYPE

This interesting group of nine patients, three of whose records are shown in Table 3, and one, Case 3, in Figure 3, included three cases of acute endocarditis and one case of acute pericarditis. The others were diagnosed chronic rheumatic heart disease. Seven of these children died during the course of observation; two were taken from the hospital and lost track of.

This group exhibited symptoms, signs and necropsy findings of marked valvular lesions, fibrinous, effusive or adherent pericarditis, or a combination of these; considerable cardiac hypertrophy; anemia and undernourishment; sometimes jaundice and fever, and lack of improvement after long rest in bed. In some there was a history of previous decompensation.

Disappearance time was decreased about equally in arm and leg over considerable periods of time, though edema, when present at all, was always minimal and then frequently occurred first in the face or in the sacral region. Later, moderate ascites or scrotal edema sometimes developed but edema of the legs was absent or minimal. These children did not show clinical evidence of decompensation at the time of death, which resulted from either myocardial failure or pulmonary complications.

The nearly equal diminution in disappearance time in arm and leg in this group resembled the results obtained by Aldrich and McClure [2] in cases of parenchymatous nephritis, but in our cardiac cases the urine either was normal or contained only small amounts of albumin (with

TABLE 3.—*Generalized, or Toxic, Type*

Case; Age	Date, 1925	Forearm: Palpable Edema	Forearm: Disappearance Time	Calf: Palpable Edema	Calf: Disappearance Time	Urine	Clinical Notes
1 10 years	1/19	0	60 min.+	0	60 min.+	Normal	Precordial pain; pallor; hemoglobin 60% (Tallquist); pericardial and thoracic effusion
	1/24	0	41 min.	0	30 min.	Albumin + Leukocytes ++	Slight dyspnea; normal blood chemistry
	2/ 2	0	54 min.	0	53 min.	.....	No dyspnea; less pericardial and pleural fluid
	2/13	0	31 min.	0	22 min.	Normal	Dyspnea, cyanosis and moderate fever
	2/17	0	23 min.	0	22 min.	Normal	Vomiting; Cheyne-Stokes respiration
	2/18	....	.....	....	.....	.....	Died; necropsy; adhesive pericarditis; healed rheumatic endocarditis; passive congestion of the kidneys
	1924						
2 8 years	11/ 1	0	49 min.	0	48 min.	....	Pallor; emaciation; moderate fever; palpable liver and spleen; hemoglobin 70% (Tallquist)
	11/13	0	34 min.	0	42 min.	Normal	
	11/21	0	27 min.	0	26 min.	.....	Dyspnea; fever; sacral edema; ascites; spleen larger; hemoglobin 47%; red blood cells, 3,900,000
	11/28	0	34 min.	0	33 min.	Normal	Right hemiplegia (embolic)
	12/ 2	0	20 min.	0	35 min.	Normal	Fever; less dyspnea; no ascites
	12/12	0	29 min.	0	28 min.	.....	Hemoglobin 35% (Dare)
	12/23	0	28 min.	0	26 min.	.....	Marked pallor; petechial hemorrhages
	1925						
	1/ 5	0	46 min.	0	26 min.	.....	Prostration and continued fever
	1/14	....	.....	....	.....	.....	Died; necropsy; no edema; thrombo-ulcerative endocarditis; anemic infarcts and lymphocytic infiltration of kidneys
	1924						
3 9 years	9/ 1	0	49 min.	0	60 min.	.....	Dyspnea; pallor; enlarged liver
	9/23	0	60 min.	0	60 min.	.....	No dyspnea
	10/ 7	0	60 min.+	0	60 min.+	.....	Up part of day
	10/23	0	60 min.	0	60 min.+	.....	
	11/10	0	60 min.+	0	60 min.+	.....	Up all day; home November 19
	12/ 6	....	.....	....	.....	.....	Returned to hospital on account of vomiting attacks
	12/ 8	0	60 min.	0	60 min.	.....	
	12/22	0	45 min.	0	43 min.	Albumin ++ Casts 0	Face puffy
	12/29	+?	22 min.	+	21 min.	Albumin +++, casts 0	Cyanosis; pericardial friction rub
	1925						
	1/ 5	0	40 min.	+	26 min.	Albumin +	Scrotal edema
	1/10	0	32 min.	+	31 min.	Albumin +	No facial or scrotal edema
	1/17	0	25 min.	+	24 min.	Normal	Recurrent facial edema
	1/24	0	28 min.	+	26 min.	Albumin +++, casts 0	Extreme pallor; dyspnea; irregular pulse; normal blood chemistry
	1/25	....	.....	....	.....	.....	Died; clinical diagnosis: chronic pericarditis and endocarditis

exception of in Case 3, Table 3) and a few casts, red cells being absent. The nitrogenous elements of the blood, when determined, were within normal limits. Necropsy, in the several cases in which it was permitted, confirmed the diagnosis of cardiac disease; the kidneys were usually passively congested but otherwise normal.

From the fact that all but two of these patients, in whom there was a generalized decrease in disappearance time, died during the period of observation, it would appear that the intradermal test is of considerable confirmatory value in rendering an unfavorable prognosis in this type of cardiac case.

COMBINED DECOMPENSATION AND TOXIC TYPE

Five children who had chronic rheumatic heart disease or acute pericarditis demonstrated during certain periods of their course an equal shortening of disappearance time in arm and in leg. The records of three of these are given in Table 4, and of one of these, Case 3, in Figure 4. Edema was either absent or slight and confined to the face or the sacral region; sometimes there was moderate ascites. As an intermediary or more often as a terminal event, cardiac decompensation with edema occurred, and the disappearance time changed to the type described for the decompensation group; i. e., it became much less in the edematous leg than in the nonedematous or slightly edematous arm.

In two of the patients, tests were performed from two to five hours after death, and the time of disappearance, in regions of pitting edema, was found to be short—about the same as it had been during life.

These children resembled those of the preceding toxic group. They were clinically severe cases of cardiac disease, and unresponsive to treatment; death occurred in all. Clinical or necropsy findings, or both, established the presence of cardiac disease and absence of kidney involvement, except for chronic passive congestion, and in Case 2 cloudy swelling.

COMMENT

The decreased disappearance time of the intradermally injected salt solution probably indicates an increased water affinity of the adjacent tissues. This increased water affinity doubtless depends on an abnormal state of the tissues.

By means of the intradermal salt solution test those cardiac cases which exhibit a decreased disappearance time are separated into two groups from the standpoint of location of this tissue disturbance. In the first group there is a localized tissue disturbance, chiefly at the site of edema, and a definite cardiac decompensation; in the second group, a generalized tissue disturbance and no cardiac decompensation.

TABLE 4.—*Combined Type*

Case; Age	Date, 1924	Forearm: Palpable Edema	Forearm: Disappearance Time	Calf: Palpable Edema	Calf: Disappearance Time	Urine	Clinical Notes
1	8/24	0	50 min.	0	60 min.+	.....	Bed rest; no dyspnea
8 years	9/16	0	55 min.	0	54 min.	.....	
	9/27	0	39 min.	0	60 min.	.....	
	10/16	0	60 min.	0	45 min.	.....	Edema over sacrum
	10/20	0	48 min.	0	35 min.	.....	
	10/24	0	41 min.	0	39 min.	.....	Dyspnea; rapid pulse; sacral edema
	10/27	0	49 min.	0	47 min.	.....	Puffiness of face
	11/ 3	0	28 min.	+	18 min.	.....	Enlarged liver; ascites?
	11/ 8	0	23 min.	+	11 min.	Normal	Ascites and vulval edema
	11/13	0	48 min.	++	10 min.	.....	Right hydrothorax
	11/25	0	37 min.	++	11 min.	Normal	Puffy face; dyspnea; cyanosis
	11/28	0	44 min.	++	6 min.	.....	Precordial pain
	12/ 2	+	32 min.	+++	1 min.	.....	
	12/ 8	+	21 min.	+++	20 sec.	.....	Marked dyspnea
	12/ 9	....	.....	....	.....	.....	Died; clinical diagnosis: adhesive pericarditis and chronic endocarditis
2	10/ 1	0	45 min.	+	5 min.	Albumin ++ Casts +	Dyspnea and enlarged liver
12 years	10/ 5	0	24 min.	+	8 min.	.....	Dyspnea
	10/ 7	0	53 min.	+	15 min.	Albumin +	No dyspnea
	10/ 9	0	50 min.	0	27 min.	.....	Jaundice and fever
	10/14	0	60 min.+	0	43 min.	Albumin +	Decreased jaundice
	10/22	0	60 min.+	0	56 min.	Albumin ++	No jaundice; recurrent fever
	10/27	0	32 min.	0	30 min.	.....	Gain in weight
	11/ 1	0	43 min.	0	28 min.	.....	Subicteric
	11/ 3	0	32 min.	0	30 min.	.....	Jaundice; no dyspnea
	11/ 8	0	36 min.	0	26 min.	Albumin +	Jaundice
	11/10	0	38 min.	0	37 min.	Normal	Jaundice decreased; ascites?
	11/19	0	31 min.	0	29 min.	Albumin +	
	11/28	0	46 min.	0	50 min.	Normal	No jaundice; up part of day
	12/ 2	0	36 min.	0	35 min.	.....	
	12/12	0	56 min.	0	54 min.	.....	Up most of day
	12/29	0	40 min.	0	38 min.	Albumin +	Acute pharyngitis
	1925						
	1/14	0	50 min.	0	49 min.	Normal	Up and about
	1/26	0	54 min.	0	53 min.	Normal	
	2/ 2	0	60 min.+	0	60 min.+	.....	
	2/14	0	28 min.	0	37 min.	.....	Slight fever; no other symptoms
	2/15	....	.....	....	.....	.....	Home
	4/26	....	.....	....	.....	.....	Readmission to hospital; dyspnea; vomiting; jaundice; ascites; large liver
	4/27	0	17 min.	++++	5 sec.	.....	Hemoglobin 75% (Tallquist)
	4/29	+	3½ min.	++++	2 sec.	Albumin + Casts +	Normal blood chemistry
	5/ 4	++	12 min.	++++	1 sec.	.....	Marked dyspnea and cyanosis
	5/ 9	....	.....	....	.....	.....	Died; necropsy: chronic rheumatic endocarditis; mitral stenosis; cloudy swelling of kidneys
5 hours postmortem		+++	4 min.	++++	1 sec.	.....	Test made on cadaver
3	2/19	0	42 min.	0	31 min.	Albumin +	Admitted to hospital; dyspnea; pallor; large liver
7 years	2/23	0	23 min.	0	22 min.	.....	No dyspnea
	2/28	0	40 min.	0	39 min.	.....	Scrotal edema
	3/ 9	0	25 min.	0	24 min.	Normal	
	3/16	0	43 min.	0	43 min.	.....	Persistent pallor
	3/23	0	29 min.	0	21 min.	.....	Scrotal edema
	4/ 4	0	38 min.	0	37 min.	Normal	
	4/14	0	43 min.	0	42 min.	Normal	Precordial pain
	4/27	0	60 min.	0	50 min.	Albumin+ Casts 0	Normal blood chemistry
	5/ 4	0	39 min.	0	17 min.	.....	Precordial pain; sacral edema
	5/11	0	40 min.	0	29 min.	Normal	
	5/15	0	43 min.	+	24 min.	Albumin +	Face puffy; dyspnea
	5/19	0	27 min.	++	27 min.	Albumin +	Increased dyspnea
	5/23	0	20 min.	+++	4 min.	Albumin + Casts +	Rapid and weak pulse
	5/26	0	20 min.	+++	2½ min.	.....	Scrotal and facial edema
	5/30	+	9 min.	+++	1 sec.	.....	Marked dyspnea
	5/31	....	.....	....	.....	.....	Died; necropsy: adhesive pericarditis and rheumatic endocarditis; passive congestion of kidneys
2½ hours postmortem		+	31 min.	+++	1 sec.	.....	Test made on cadaver

The intradermal salt solution test in the latter class gives results as regards distribution of tissue disturbance comparable to those found by previously mentioned workers in cases of parenchymatous nephritis, scarlet fever and lobar pneumonia. Baker,[3] working with cases of scarlet fever and diphtheria, suggested intoxication as the cause of a generalized tissue disturbance resulting in diminished disappearance time. Harrison[4] offered a similar hypothesis for her results with the test in lobar pneumonia. Anemia of the tissues was advanced by Lazarus-Barlow,[6] in 1895, as a cause of localized or generalized edema.

CONCLUSIONS

In a group of forty-seven children with rheumatic heart disease, or allied conditions, it was found that:

1. The disappearance time of intradermally injected salt solution was normal (above fifty minutes) in well compensated nontoxic cardiac disease, acute rheumatic fever and chorea.

2. In cardiac decompensation with edema, shortening of disappearance time was limited to edematous and preedematous regions and was noted earliest in the dependent parts of the body.

3. Decrease in disappearance time did not precede other clinical signs of impending decompensation with sufficient constancy to make the test of much value in predicting a break in compensation.

4. In certain severely ill patients having cardiac disease without decompensation there was a marked and nearly equal decrease in disappearance time in arm and leg.

5. The intradermal salt solution test was of value in this generalized or toxic group in rendering an unfavorable prognosis.

6. The disappearance time picture characteristic of the toxic group was altered in the direction of that characteristic of the decompensation group, if cardiac decompensation developed.

7. In two patients tested after death, the disappearance time in edematous parts was practically as short as during life, which demonstrated that, under these conditions, circulation of the blood was not necessary in the phenomenon of disappearance of intradermally injected salt solution.

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6. Lazarus-Barlow, W. S.: The Pathology of Edema, Brit. M. J. **1**:634; 691, 1895.

EXCRETION OF PHENOLSULPHONEPHTHALEIN IN OBSTRUCTIVE JAUNDICE *

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Whatever the manner in which the normal kidney performs its functions of excreting water, salt, nitrogenous products and foreign dyestuffs like phenolsulphonephthalein, there is not much question that when the kidneys are diseased there is often dissociation of these functions. The importance of the ability of the kidney to excrete phenolsulphonephthalein is particularly emphasized by those cases in which there is a marked diminution of dye excretion while the blood nitrogen figures are normal, or at the upper limit of normal, with the water excretion undiminished. Without discussing the clinical syndromes giving rise to these combinations of expressions of kidney function (not of kidney morphology), it will be assumed that the rate of excretion of phenolsulphonephthalein is one criterion of renal function.[1] And when there is evidence of dysfunction, one method that may aid in estimating diminution of function is the dye excretion.

That there is a relationship between obstructive jaundice and renal disease has been recognized for many years. Certainly significant but as yet not understood, are the changes in kidney morphology in obstructive and toxic jaundice. A recent discussion of the influence of jaundice on the morphology of the kidney is that by Haessler, Rous and Broun.[2] Quoting Quincke, they emphasize that the distribution of bile pigments is first in the cortex and, as the jaundice persists, there is an increase in the number of pigment granules in the cells of the convoluted tubules and the loops of Henle. Together with many free granules, yellow, green or brown casts then collect in the lumina of the loops. In addition there is cloudy swelling, loss of the brush border, and even necrosis of the tubular epithelium. The glomeruli remain practically unstained.

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2. Haessler, H.; Rous, P., and Broun, G. C.: The Renal Elimination of Bilirubin, J. Exper. Med. **35**:533 (April) 1922.

Haessler and his associates further discuss their own observations. They point out that the urinary sediments of jaundiced dogs and human beings contain cells of renal origin which are deeply bile stained. This renal pigmentation is believed to be specific evidence of renal injury, and not an expression of sojourn in the bile stained urine. Their statement, "After long continued jaundice in man the urinary sediment yields striking indication of the serious condition of the kidneys," is not to be regarded lightly because of the infrequency of diminution of renal function as expressed by our usual tests. In spite of the presence of renal injury, these cases of obstructive jaundice, in the majority of instances, have no evidence of impaired function. Henke and Lubarsch [3] describe as the precursors of bile casts coagulated masses in Bowman's capsule. These masses, which are chiefly made up of coagulated protein, are found in the lumina of the tubules, which are dilated and flattened. They state that the epithelium of the proximal convoluted tubules shows marked vacuolization, albuminous degeneration and coagulation necrosis. The blood vessels are normal. There is, however, a group that have nitrogen retention, and in which there is often a terminal uremia.[4] This group will be discussed later. Careful search of the literature has revealed that the excretion of phenolsulphonephthalein has not been reported for cases having normal or abnormal blood nitrogen figures.

The excretion of the dye in obstructive jaundice is important chiefly for these reasons:

1. It is a rapid method of estimating a renal function. If the dye excretion were low in a case of obstructive jaundice, extensive operative procedures would be carefully guarded against. A normal dye excretion assures the operator that kidney function is most probably normal, and the dangers of postoperative complications through renal disease are less likely.

2. In cases of jaundice complicated by increased or lowered blood nitrogen figures, it may be possible by determination of the dye excretion to present additional evidence for or against the presence of disturbance in renal or hepatic function. The French students of jaundice, for example, have suggested that an increase of blood urea, up to a certain point at least, may be due to hyperfunction of the liver.[5] Walters and Parham,[4] in their report from the Mayo Foundation, state that "in a large percentage of cases of obstructive jaundice after the anesthesia was used, the blood urea became double the preoperative

3. Henke, F., and Lubarsch, O.: Handbuch der Speziellen Pathologischen anatomic und histologie **6**:281-285, Berlin, Julius Springer, 1925.

4. Walters, W., and Parham, D.: Renal and Hepatic Insufficiency in Obstructive Jaundice, Surg., Gynec. & Obst. **35**:605-609 (Nov.) 1922.

5. Cumston, C. G.: Icterus Gravis, New York M. J. **113**:200-201, 1921.

value the second or third day after operation. If after operation there is an increase in the cholangeitis, or if biliary drainage becomes insufficient, there may be a concomitant increase in nephritis with rising blood urea. These patients sometimes show an alarming picture of uremia and may not recover." A number of typical cases is presented and discussed.

With the intense jaundice of the acute toxic atrophies of the liver, such as acute yellow atrophy [6] and arsphenamin [7] poisoning, there have been reported changes in the urea nitrogen of the blood. The low figures, that is, those which are at the lowest limits of normal, are believed to be the result of diminished urea formation by the liver incidental to the destruction of its parenchyma. This is typical of acute yellow atrophy of the liver. In arsphenamin poisoning both low and high figures are found for the urea in the blood, the former probably occurring in the more fulminating liver injuries. In this group of cases of jaundice degenerative lesions are found in the kidneys. The urea nitrogen in the blood may not be taken here as a criterion of renal function because of abnormal urea metabolism, and therefore in this group the determination of the phenolsulphonephthalein excretion may be an important aid in studying renal function.

Before the dye excretion in the presence of jaundice may be evaluated when blood nitrogen changes are present, the influence of jaundice alone on the phenolsulphonephthalein excretion must be known. It is the purpose of this article to report such a control series of cases of jaundice which were uncomplicated by changes in blood nitrogen and which had normal water excretion.

METHOD

The phenolsulphonephthalein was readily determined in the presence of the bile pigments by precipitating the extraneous pigment with an excess of saturated barium hydroxid. This procedure has recently been reported.[8] In urine containing bile pigments, the dye is partially adsorbed during precipitation, the degree of adsorption being dependent on the concentration of pigments and total urine volume. The correction for adsorption is easily determined because the quantity of adsorbed phenolsulphonephthalein in a given specimen of urine whose pigments have been precipitated by barium hydroxid, as far as the accuracy of the test requires, is a constant within the limits of from 0 to 6 mg. (0 to

6. Stadie, W. C., and Van Slyke, D. D.: Effect of Acute Yellow Atrophy on Metabolism and on Composition of Liver, Arch. Int. Med. **25**:693-704 (June) 1920.

7. Bailey, C. V., and McKay, A.: Toxic Jaundice in Patients Under Antisyphilitic Treatment, Arch. Int. Med. **25**:628-647 (June) 1920.

8. Abramson, H. A.: The Determination of Phenolsulphonephthalein in the Urine in Jaundice, Arch. Int. Med. **34**:714-720 (Nov.) 1924.

100 per cent.) of the dye. For further theoretical considerations the original paper dealing with the method of determination should be consulted. The details of the method of determination of the dye are given below.

The method devised from the studies on adsorption differs from the routine as follows: When there is no correction for adsorption:

1. It is preferable to give the dye intravenously but intramuscular injection is almost as suitable.

2. The two hour specimen should be divided into two equal parts.

3. To one part an excess (urine volume plus 50 c. c.) of saturated barium hydroxid should be added, and this should be diluted to 500 or 1,000 c. c. and then filtered. A portion of the filtrate should be compared with standards. If the 500 c.c. dilution is used, the reading is direct. If 1,000 c.c. is the dilution, the two hour excretion is the reading times 2. It is, of course, only necessary to catch a few cubic centimeters of the filtrate. The dilution to 2 liters aids in colorimetric comparison.

4. If the total two hour percentage of excretion of dye is normal or only 5 or 10 per cent. below the lower limits of normal, the reading stands as the excretion of the dye and the excretion may be considered normal.

When correction for adsorption must be determined:

5. If the reading obtained is below normal, it must be determined whether the diminished excretion of the dye is actual or is due to adsorption. To the remaining half of the urine, of which the dye content has been determined, 0.25 c.c. (for 500 c.c. dilution) or 0.5 c.c. (for 1,000 c.c. dilution) of phenolsulphonephthalein should be added. With intense jaundice and large urine volume the latter is preferable. The percentage of dye in this control should be redetermined.

6. The second reading in Paragraph 5 minus the first reading in Paragraph 4 gives the quantity of dye not adsorbed. For example, if the first reading (apparent two hour excretion) had been 20 per cent. and if to the remaining portions 0.25 c.c. of the dye had been added, the second reading, granting that none had been lost by adsorption, would be 20 per cent. plus 50 per cent. (0.25 c.c. of dye to 500 c.c.), or 70 per cent. If the reading were 50 per cent., instead of 70 per cent., it would be evident that the added dye gave only an additional 50 per cent. minus 20 per cent., or 30 per cent. of color. Hence, three-fifths of the dye added was determined and two-fifths lost by adsorption.

7. The final corrected reading of excreted dye is equal to the first reading divided by the fraction not adsorbed, or

$$\frac{20 \text{ per cent.}}{3/5} = 20 \text{ per cent.} \times 5/3 = 33 \text{ per cent.}$$

Case	Age, Yrs.	Clinical Diagnosis	Confirmed Diagnosis	Duration of Jaundice	Urine	Phenol-sulphone-phthalein, Two Hour Excretion	Water Salt Retention	Blood Nitrogen	Mg. per 100 C.c. Blood Cholesterol	Van den Bergh		Remarks
										Direct	Indirect	
1	40	.....	Multiple neoplasms	5 wk.	Bile ++++; albumin, trace; hyaline casts; granular casts	40% (intravenous)	None	Normal	0.254	Pos.	1:12,000	
2	54	.....	Neoplasms with liver metastases	3 wk.	Bile ++++; otherwise negative	50% (intramuscular)	None	Normal	0.142	Pos.	1:5,000	
3	23	Catarrhal jaundice	.....	2 wk.	Bile ++++; otherwise negative	35% (intramuscular)	None	Normal	Cholesterinemia	Pos.	1:6,000	
4	45	Carcinoma of bile duct	.....	2 wk.	Bile ++++; otherwise negative	40% (intramuscular)	None	Normal	0.130	Pos.	1:16,000	
5	24	.....	Hodgkin's disease	5 wk.	Bile ++++; otherwise negative	60% (intramuscular)	None	Not ascertained	Not ascertained	Pos.	1:16,000	
6	36	Infectious jaundice	.....	?	Bile ++++; urobilin, negative; albumin, trace; hyaline and granular casts	60% (intramuscular)	None	Normal	0.190	Not done	1:10,000	Developed secondary nephritis with 0% dye and azotemia
7	50	Neoplasm with common duct obstruction	.....	3 wk.	Bile ++++; albumin, trace; hyaline and granular casts	45% (intramuscular)	None	Normal	0.200	Pos.	1:10,000	
8	35	.....	Common duct stone	3 wk.	Bile ++++; albumin, faint trace; sugar, negative	50% (intramuscular)	None	Not ascertained	Not ascertained	Pos.	1:6,000	
9	12	.....	Malignant neoplasm	4 mo.	Bile ++++; albumin, trace; granular casts	60% (intravenous)	None	Normal	0.294	Pos.	1:4,000	
10	34	.....	Adenocarcinoma about ampulla of Vater	6 mo.	Bile ++++; otherwise negative	40% (intramuscular)	None	Not ascertained	Not ascertained	Pos.	1:3,300	
11	50	Neoplasm of duct	.....	5 wk.	Bile ++++; otherwise negative	50% (intramuscular)	None	Normal	0.230	Pos.	1:20,000	
12	42	.....	Toxic jaundice (arsphenamin)	5 wk.	Bile ++++	50% (intramuscular)	None	Normal	0.100	Pos.	1:30,000	
13	51	Postoperative adhesions ?	.....	10 wk.	Bile ++++; occasional hyaline casts	65% (intravenous)	None	Normal	0.130	Pos.	1:8,000	Postcholecystectomy
14	45	Catarrhal jaundice ?	.....	3 wk.	Bile ++++; otherwise negative	65% (intravenous)	None	Normal	0.136	Pos.	1:20,000	Incomplete obstruction
15	72	.....	Carcinoma of pancreas	2 wk.?	Bile ++++; albumin, trace; hyaline and granular casts	65% (intravenous)	None	Normal	0.100	Pos	1:6,000	Hypertension atherosclerosis

In the event that the colorimetric comparison is not good because the pigment has not all been removed, practically the last traces may be precipitated by making a second dilution using barium hydroxid instead of water as the diluent. The second dilution does not cause much adsorption of dye because the mass of precipitate is usually small. Furthermore, the colorimetric comparison with standards above 30 per cent. has been difficult, and the most accurate readings are obtained by comparison with lower values and by then multiplying by the necessary correction factor.

SUMMARY OF RESULTS AND COMMENT

The phenolsulphonephthalein excretion was found to be normal in fifteen cases of obstructive jaundice with a varied etiology. In all of these cases there was no evidence of renal insufficiency. The duration of jaundice was up to six months. Seven cases had periods of intense icterus lasting more than one month. Three of these lasted more than two months. The ages ranged from 12 to 72 years (accompanying table).

It would seem from the morphologic changes in the kidney in jaundice that the degenerative processes are to be found chiefly in the convoluted tubules. In uncomplicated obstructive jaundice, the excretion of phenolsulphonephthalein is normal. This normal excretion of the dye would fit in with the hypothesis that the excretion takes place through the glomeruli of the kidney, since there is apparently no evidence that the severe renal poisons that are present in jaundice influence the structure of the glomeruli.

These prolonged cases of jaundice demonstrate that in uncomplicated obstructive jaundice kidney function as estimated by the foregoing methods is probably unimpaired. What is the influence, then, of obstructive jaundice on diseased kidneys that are functioning normally but whose reserve is near the point at which additional injury may produce diminished function? Are the cases of obstructive jaundice which develop uremia those in which a further slight kidney injury leads to renal dysfunction? And finally the question arises, Is this injury simply due directly to the action of bile pigments and salts on the kidney, or is it due to a disturbance of the total metabolism?

CONCLUSIONS

1. The excretion of phenolsulphonephthalein by the kidneys in obstructive jaundice has clinical and physiologic significance.

2. In fifteen cases of uncomplicated obstructive jaundice the excretion of phenolsulphonephthalein was found to be normal.